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VOLUME XXV NUMBER 3

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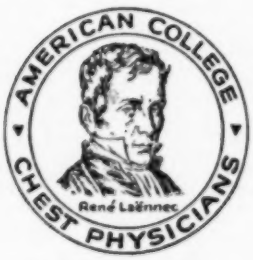

PUBLISHED MONTHLY

MARCH
1954

PUBLICATION OFFICE, ALAMOGORDO ROAD, EL PASO, TEXAS
EXECUTIVE OFFICE, 112 EAST CHESTNUT STREET, CHICAGO 11, ILLINOIS

Entered as Second Class Matter August 18, 1936, at the Postoffice at El Paso, Texas
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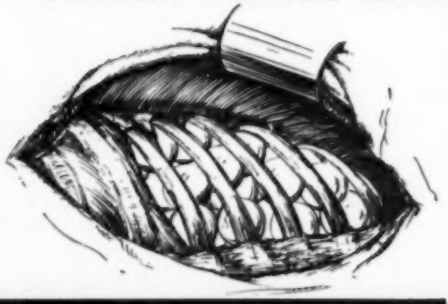

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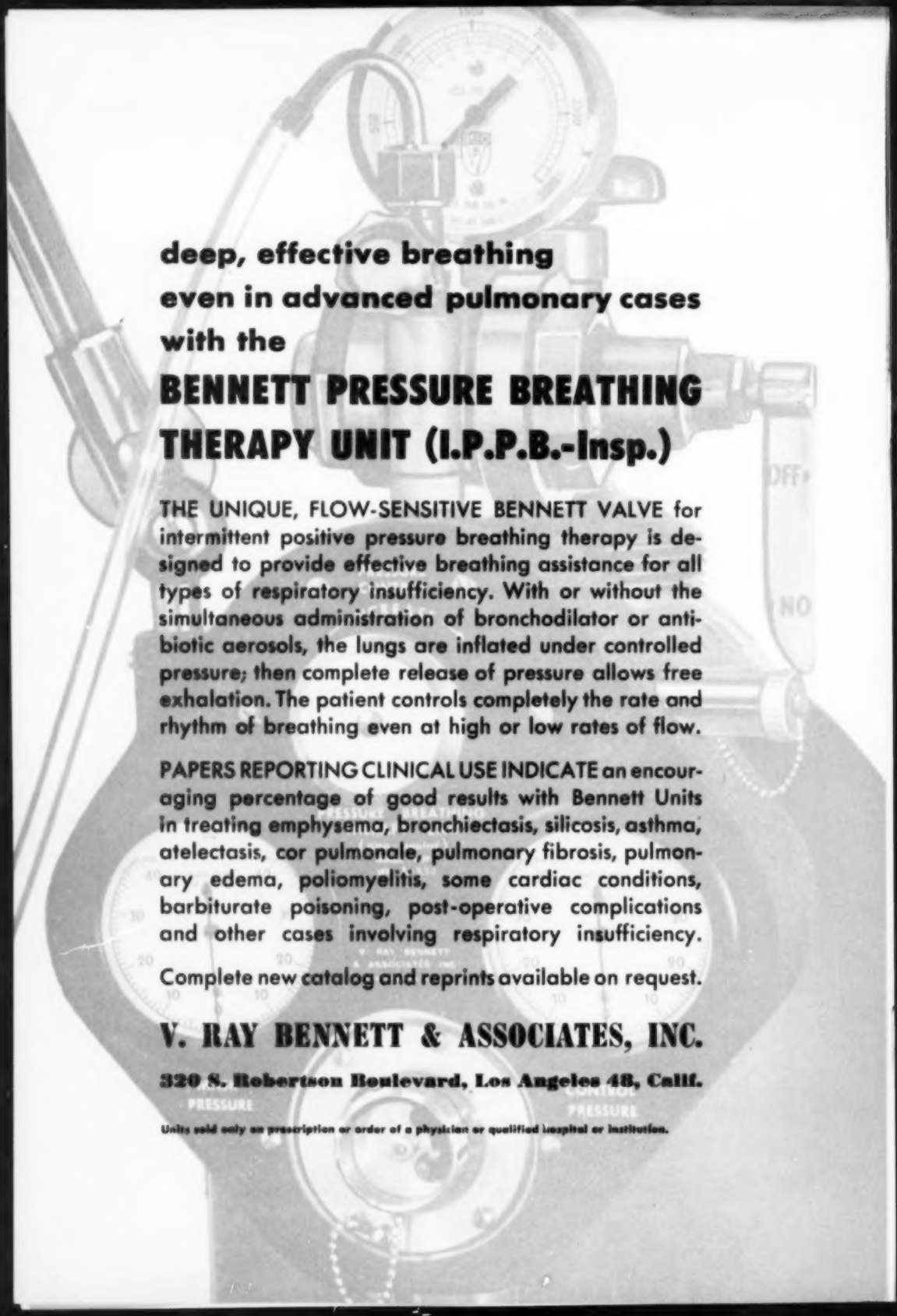

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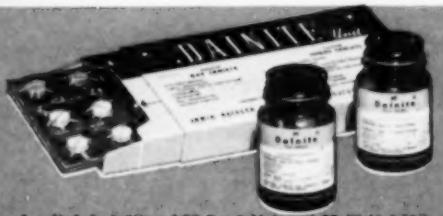

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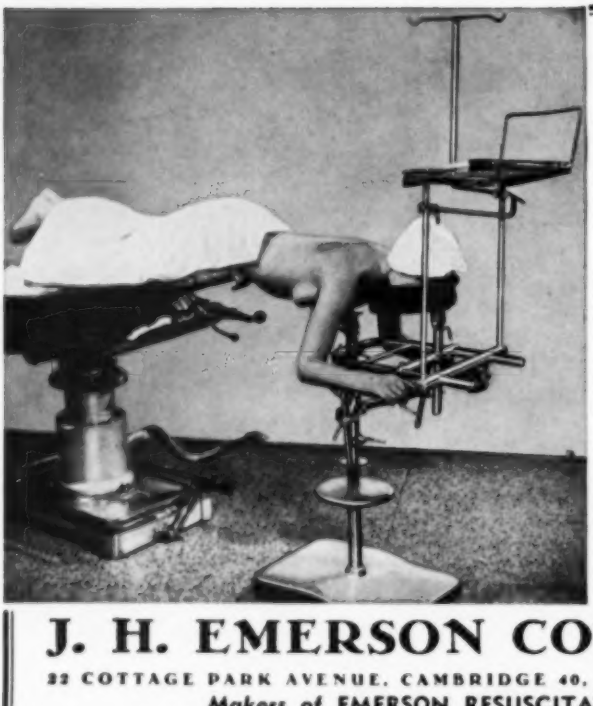

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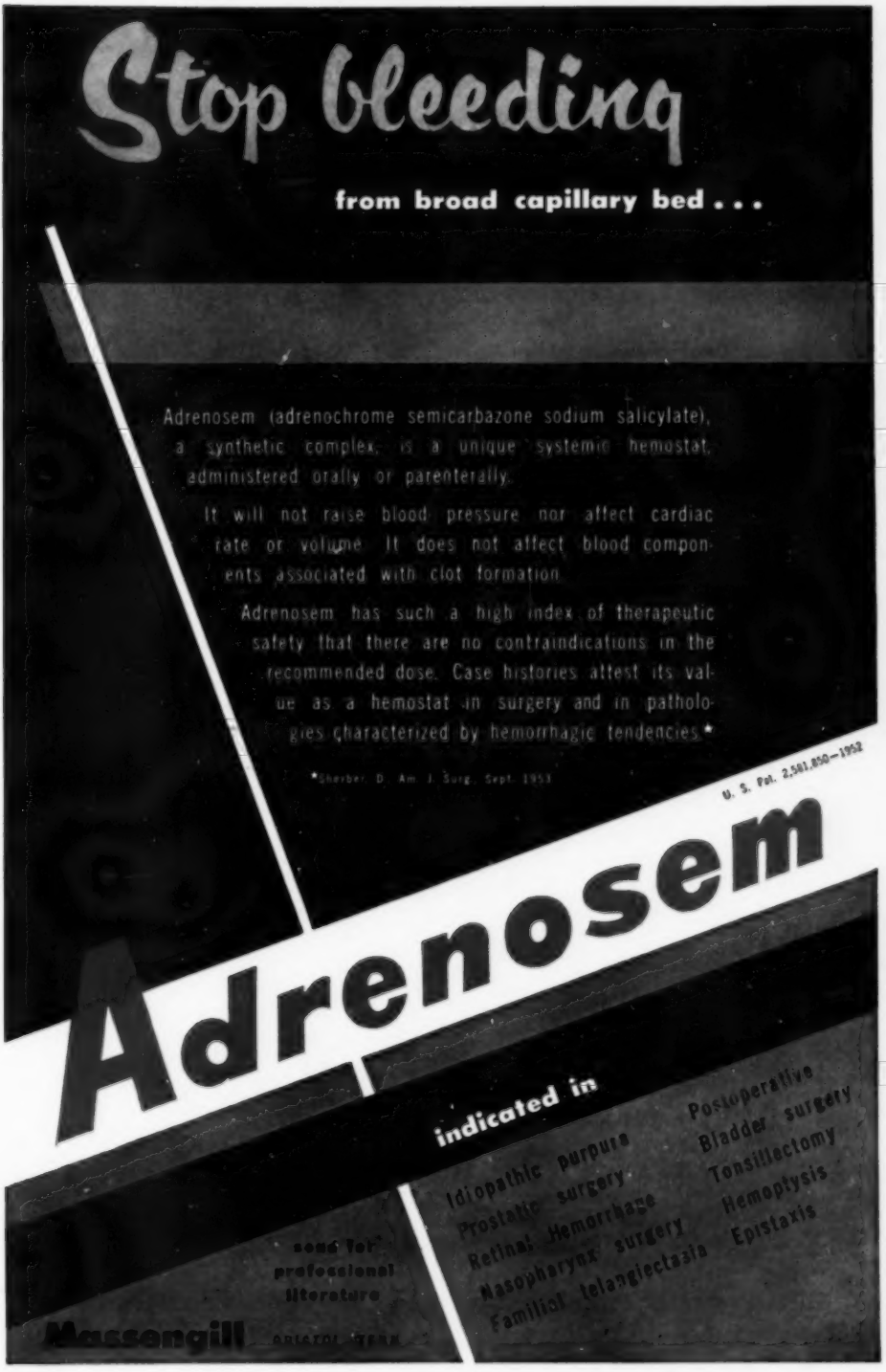
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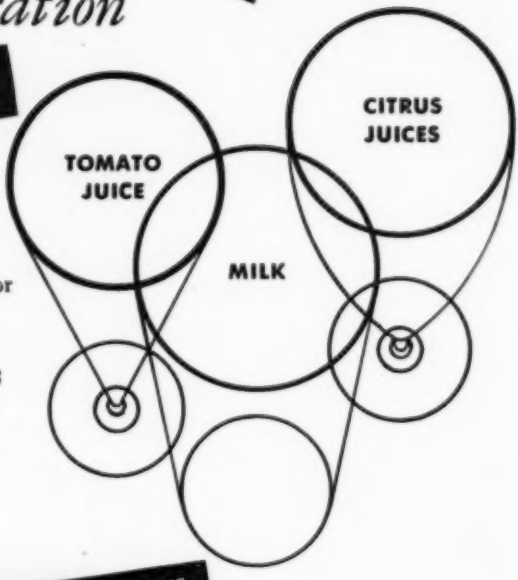

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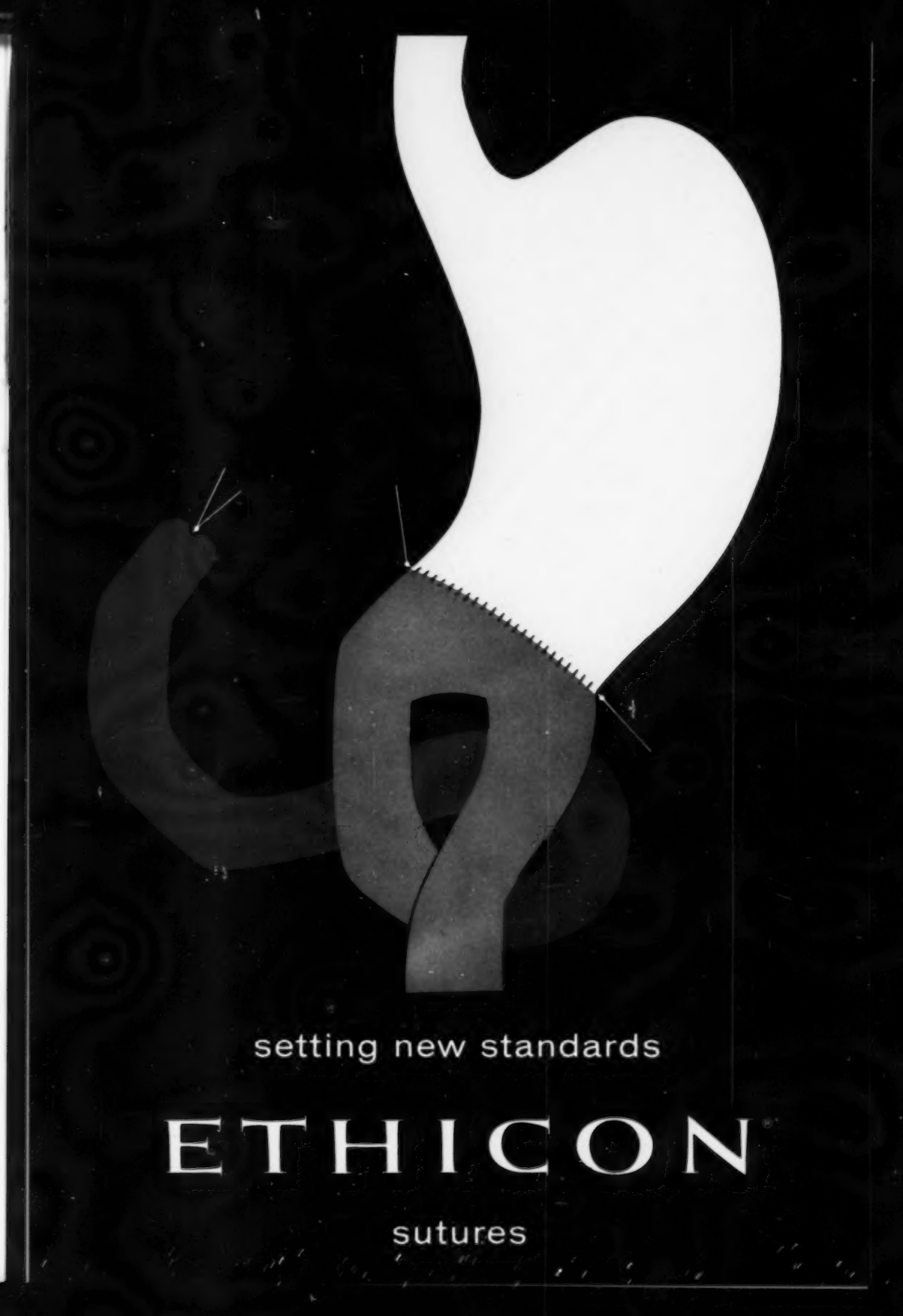
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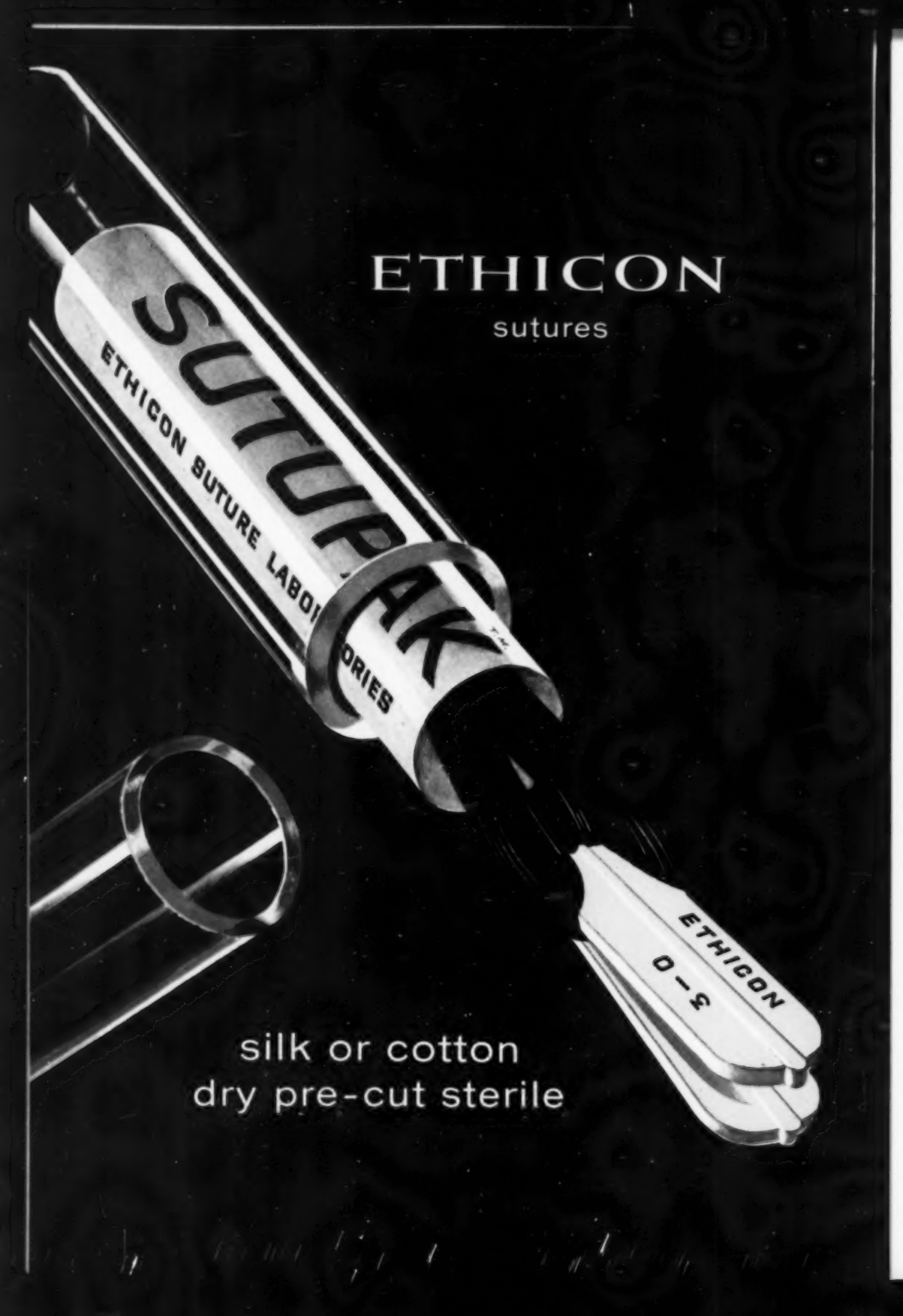
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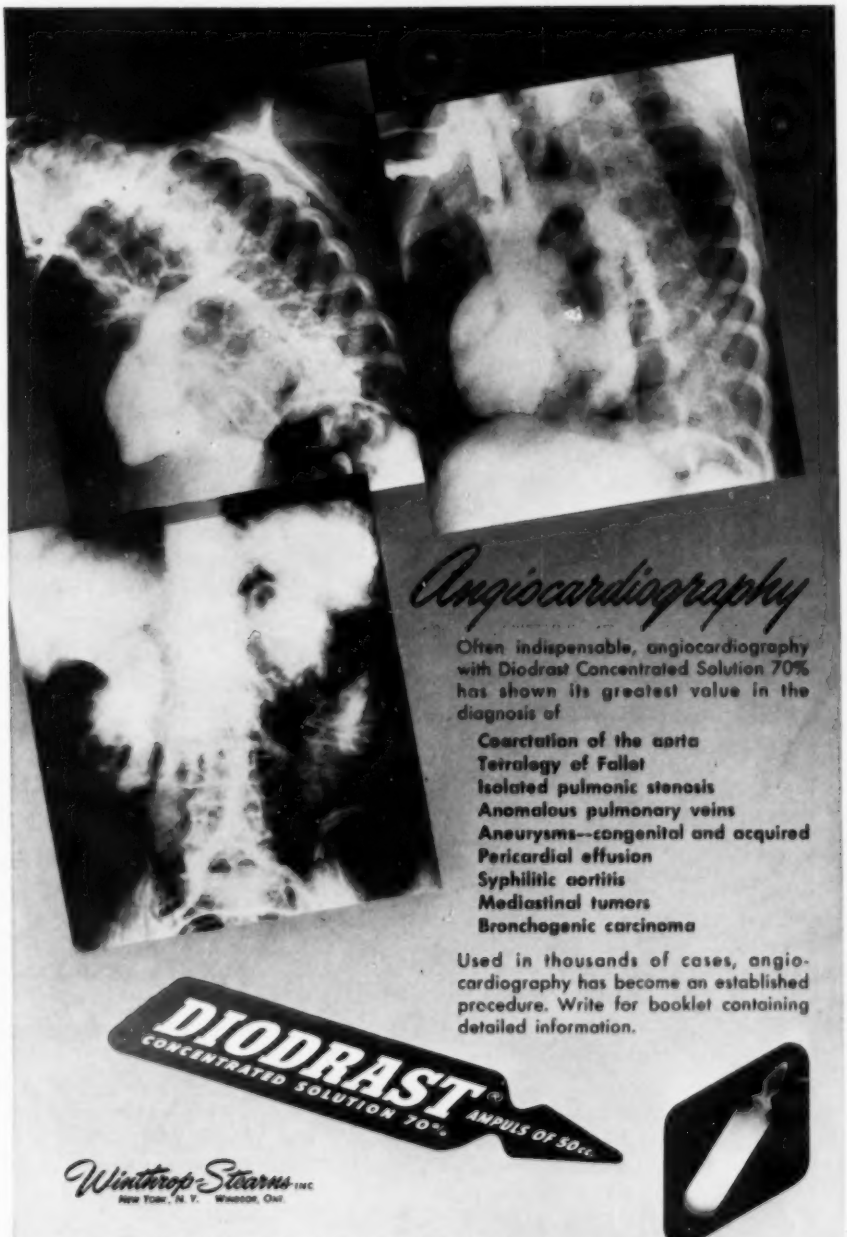
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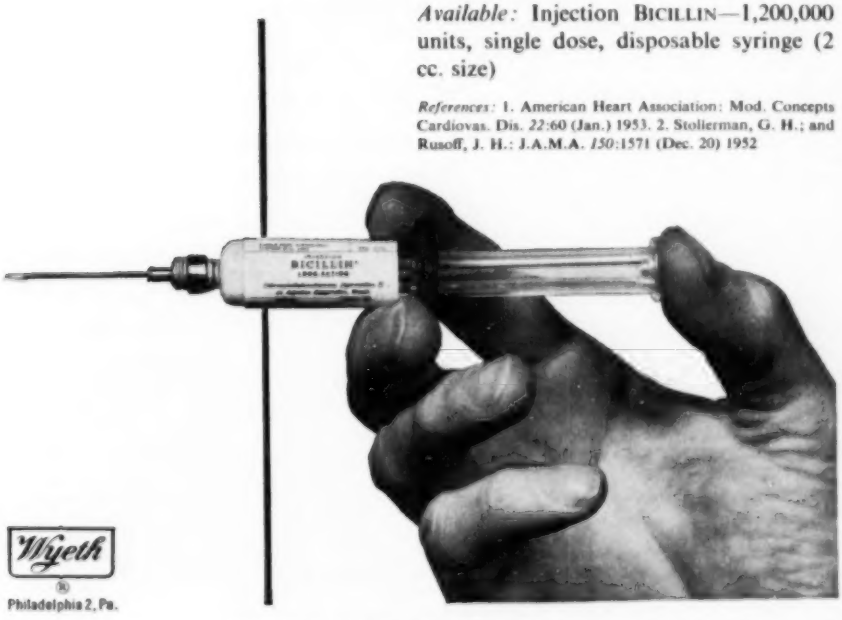

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VOLUME XXV MARCH 1954 NUMBER 3

Introduction

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Concomitant disturbances of pulmonary and cardiovascular function often occurs with disease of either of these systems. Likewise, alteration in the metabolism and possibly enzyme systems often occurs as a result of the functional disturbances which are observed in such diseased states.

The problems which challenge the clinicians and physiologists are: (1) the diagnosis of the primary defect as either pulmonary or cardiovascular, (2) the development of methods for measuring and assaying the importance of the dysfunction of either system, (3) the factors responsible for the induction of functional or structural defects in one system as a sequel to disease in the other, (4) the prevention or correction of the secondary as well as the primary diseased state.

The several articles that will appear in this journal in a portion of the symposium on cardiovascular disease are directed toward summarizing the current knowledge in this field. By such means the reader will become acquainted with the progress that has been made toward the solution of these intricate and important problems.

Measurement of Respiratory Function in Cardiac Disease: A Review

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The recent interest in abnormal cardiovascular physiology, inspired by the technique of heart catheterization and by the remarkable advances in cardiac surgery, has stimulated a parallel interest in respiratory physiology. Pulmonary function tests of long standing, classified and modernized by Baldwin et al.[1] have been found useful in the evaluation of dyspnea

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This study was supported by the Los Angeles Heart Association and the Los Angeles County Hospital Attending Staff Research Association.

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in the clinical and industrial fields. More recently the respiratory embarrassment of the cardiac patient has received close attention. This presentation is a review of some of the data in this field bearing upon the crucial problems: (1) Are such tests of objective value in the evaluation of the cardiac patient? (2) Can such tests distinguish between pulmonary disease and heart disease? (3) Are there patterns of abnormal pulmonary function which are characteristic of any given type of heart disease?

Studies of pulmonary function in heart disease, following the classification of Baldwin et al.[1] may be divided into the mechanical, or structural, and the alveolar-respiratory, or physico-chemical. Mechanical tests of pulmonary function consider the lungs as a bellows, and the tests are either static in type (inspiratory reserve, tidal air, expiratory reserve, residual air) or dynamic (walking ventilation, maximum breathing capacity, timed vital capacity). Alveolar-respiratory tests are concerned with the quantity and quality of gaseous exchange at the inspiratory, alveolar, capillary and tissue levels.

The hyperventilation of the cardiac patient was first emphasized by McMichael[2] in 1939. He pointed out the lack of correlation between vital capacity and cardiac output, and noted the fairly close inverse relationship between the ventilatory equivalent and cardiac output. The lower the cardiac output, the more air the patient had to breathe in order to utilize a given amount of oxygen. Although Grissom et al.[3] have similarly reported an increased ventilatory equivalent in congenital and acquired heart disease, no direct correlation with cardiac output or with pulmonary arterial pressure was made. Grissom's group of normal patients nevertheless showed a fall of the ventilatory equivalent with exercise in every case, whereas a rise of the ventilatory equivalent is the rule in abnormal subjects with low output failure. Richards[4] noted an inverse relationship between ventilatory equivalent and pulmonary artery pressure in 20 patients with rheumatic heart disease.

Here then are reproducable respiratory abnormalities of a simple type bearing directly on the problem of hyperventilation in the cardiac patient. They suggest the close alliance of the cardiac status to the ventilation of the patient but give no information about the mechanics involved.

The compartmentalization of the total lung volume into its physiological components was first extensively investigated by Hurtado et al.[5] Normal standards for inspiratory reserve, tidal volume, expiratory reserve and residual air were established and the total lung capacity was found to be closely correlated with radiological chest volume.

Altschule et al.[6] were among the first to employ Hurtado's methods in heart patients. Several of such earlier studies illustrate the confusion resulting from an attempt at the respiratory evaluation of a mixed group of cardiac patients. The data of Altschule, for example, show a great reduction in the inspiratory reserve, a moderate reduction in the expiratory reserve and an increase in the residual air in 12 patients with congestive failure due to rheumatic heart disease, hypertensive heart disease and coronary heart disease. But D. G. B. Richards et al.[7] studied patients with varying types of heart disease; their results were quite different. Those

with cardiac hypertrophy and some dyspnea on exertion showed an increase in expiratory reserve and in residual air; in mild congestive failure the above two lung volumes returned to a normal level; when the failure became advanced there was a decrease in both expiratory reserve and in residual air. In the studies of D. G. B. Richards and in those of Altschule, the striking constant feature was the reduction in the inspiratory reserve. Perhaps the variance in the findings of these two studies may be related to the heterogeneous nature of the groups of patients. Moreover, it is evident that the definition of "chronic heart failure" is grossly inadequate for physiological classification, and the groups at least should have been subdivided into right and left sided heart failure.

Not all so-called mechanical respiratory tests are abnormal in the presence of heart disease. Richards[4] noted no reduction whatever in the maximum breathing capacity in patients with rheumatic heart disease and mitral stenosis, even in those with high pulmonary artery pressure. Our own preliminary findings do not show such normal values; in our series several patients with a marked elevation of pulmonary arterial pressure showed significant decreases in maximum breathing capacity. In fact, our attention was first called to the extraordinary changes possible in the lungs of a patient with mitral stenosis during a recent mitral valvulotomy. The surgery was rendered hazardous by the complete inability of the anesthetist to collapse the left lung during the procedure. Its leathery stiffness reflected the measure of the chronic secondary pulmonary changes.

Frank et al.[5] have recently clarified at least one group of patients in relation to mechanical pulmonary function tests. Sixty-two with rheumatic heart disease and mitral stenosis were grouped into the four subdivisions of the New York Heart Association. In Group I, those without dyspnea, the inspiratory and expiratory reserve, tidal volume, the residual air, and the air velocity index (the ratio of observed to predicted maximum breathing capacity over the ratio of observed to predicted vital capacity) were all within normal limits. The intrapulmonary mixing was also normal. In Groups II and III including patients with greater degrees of disability but not in heart failure, an increase in residual air was customary; this increase counterbalanced a decrease in the inspiratory and expiratory reserve. The air velocity index was normal even in those with a wheezing type of respiration and intrapulmonary mixing was normal. In both Groups II and III the residual air increased as the tidal volume and maximum breathing capacity decreased. Finally the patients in Group IV who had the lowest vital capacity and maximum breathing capacity also had reduced inspiratory and expiratory reserve; the residual air was lower than in other groups. The residual air was not, however, lower than the control group. Unfortunately no comparable cardiovascular measurements were undertaken, such as the determination of the cardiac output and pulmonary artery pressure. Intrapulmonary mixing was normal; an occasional subject showed an abnormal air velocity index.

One obvious "mechanical" approach to the problem of dyspnea is the

measurement of the encroachment upon the respiratory mechanism by circulatory structures, such as the effect of the enlarged heart, or the role of an increased pulmonary blood volume in the reduction of pulmonary capacity. The method of Sgostrand[9] of enclosing the chest in a plethysmograph and subtracting, under given conditions, the lung volumes from the chest volume in order to obtain vascular volumes, may give directional changes over short time intervals. With such techniques Sgostrand has demonstrated the effect of the pulmonary circulation as a reserve pool in its rapid enlargement following venous obstruction in the legs. Conversely the development of shock during anesthesia is associated with a decrease of this reserve venous pool to below 1.1 liters. The more standard method of determining increased intrapulmonary blood volume is by its direct estimation by the dye dilution technique, recently developed and summarized by Lewis.[10]

Alveolar-respiratory defects in heart disease represent an even more complex problem than the simpler mechanical encroachments on pulmonary capacity. Levels of oxygenation must be analyzed at four separate levels: the inspired air, the alveolus, the lung capillaries and pulmonary vein, and the tissue level. As with the mechanical tests of pulmonary function, the findings are incomplete, especially in the lack of adequate correlation with the type and status of the heart disease present. Because of the recent marked interest in rheumatic heart disease with mitral stenosis, particularly since this valvular defect can be directly studied by surgery and indirectly by cardiac catheterization, further discussion in this paper will emphasize mitral stenosis. The abnormal cardiovascular physiology is by no means uniform, as Gorlin et al.[11] have shown. In many instances of well developed mitral stenosis (from an auscultatory standpoint) it has been shown in this laboratory[12] that the right ventricular hemodynamics may be surprisingly normal.

Three particularly informative studies have recently appeared relative to levels of oxygenation in patients with mitral stenosis. Blount et al.[13] have studied the alveolar-arterial gradient in mitral stenosis. Their studies showed normal alveolar oxygen tension but reduced arterial oxygen tension, and thus increased alveolar-arterial gradient. This slight increase became more marked with exercise. The authors believed that the decreased arterial oxygen tension was due to increased venous admixture (shunting through poorly ventilated areas), rather than to diffusion defects through the alveolar-capillary membrane.

Carroll, Cohn and Riley,[14] using the techniques of Riley[15] have just completed a most thorough investigation of the respiratory defect in mitral stenosis. Their 29 patients fell into four categories: (1) those in whom no obvious respiratory defect was present and in whom all respiratory measurements were within the normal range; (2) those with abnormalities of distribution of blood to unventilated alveoli and of gas to unperfused alveoli; (3) those with abnormalities of diffusion across the capillary alveolar membrane; and (4) those with abnormalities of both diffusion and distribution. The authors concluded that (1) abnormalities of alveolar function are closely related to pulmonary hypertension; (2) abnormalities

of distribution disclosed by an abnormal dead space ratio and an abnormal venous admixture are accompanied by decrease in vital capacity and maximum breathing capacity; (3) abnormalities of diffusion are usually not accompanied by decrease in maximum breathing capacity or vital capacity; (4) the degree of dyspnea was well correlated with abnormal respiratory functions of distribution and diffusion; and (5) impairment of distribution appeared to be related to at least minimal pulmonary edema.

The role of anoxia in the genesis of pulmonary hypertension has also been studied in mitral stenosis, following the original observations of v. Euler and Liljestrand[16] that arterial anoxia could produce hypertension in the pulmonary circulation. Stroud and Rahn[17] have reinvestigated this subject and have produced pulmonary hypertension in dogs, creating increased pulmonary vascular resistance of 25 per cent and 48 per cent by the breathing of 15 per cent and 8 per cent oxygen respectively. In seven patients with mitral stenosis, Dressler et al.[18] again noted this remarkable relationship, but in the opposite direction. The inhalation of 100 per cent oxygen in their series of patients produced an appreciable drop in pulmonary artery pressure in each case. They did not believe that the concomitant drop in heart rate was a significant factor.

The importance of increased cardiac output in anoxia has been experimentally shown by Hürlimann and Wiggers.[19] They point to the simultaneous increase in cardiac output and pulmonary artery resistance during experimental anoxia and, in fact, believe that the increased cardiac output was the chief cause of the pulmonary hypertension.

Richards[4] has recently pointed out another possible defect in oxygenation in mitral stenosis, i.e., the defect at the tissue level. He has noted that such patients frequently complain more of aching muscles than of dyspnea, and that occasionally a patient will stop exercise before becoming dyspneic, complaining that he "cannot go on". There is little doubt that such patients do have an increased arterio-venous oxygen difference as has been shown.[12] It could well be that somatic muscles are not capable of more than "optimum" tissue extraction per aliquot of blood, and that anoxia at the tissue level may be the cause of disability.

We wish to acknowledge the assistance of Mr. W. Ray Hartwig and Miss Mary Mayo for their invaluable contributions to this work.

SUMMARY

Pulmonary function tests may bring much important information to the dynamic aspects of heart disease. The ultimate goals should include relatively simple tests, first to determine the degree of pulmonary insufficiency in the patient with heart disease; second, to distinguish between pulmonary and cardiac disability; and third, to aid in the differential diagnosis of cardiopulmonary disorders.

RESUMEN

Las pruebas de la función pulmonar, pueden proporcionar muy importante información sobre el aspecto dinámico de las afecciones cardiacas. El objetivo final debe incluir la realización de pruebas relativamente sencillas con el objeto de determinar en primer lugar el grado de insu-

ficiencia pulmonar en el enfermo cardiaco y en segundo lugar, distinguir entre incapacidad pulmonar y la cardiaca. Por último, ayudar en la diferenciación de los trastornos cardiopulmonares.

RESUME

Les épreuves fonctionnelles pulmonaires peuvent apporter des renseignements très importants au sujet du retentissement des maladies du coeur.

Il s'agit d'utiliser des épreuves relativement simples (1) pour déterminer l'importance de l'insuffisance pulmonaire chez les malades atteints d'affections cardiaques; (2) pour bien faire la distinction entre trouble de la fonction pulmonaire et trouble de la fonction cardiaque; (3) pour favoriser le diagnostic différentiel des affections touchant le coeur et le poumon.

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Pulmonary Circulation: Its Relation to Normal and Altered Dynamics*

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Although the anatomic differences between the pulmonary and systemic circulations have been recognized for years and some of the functional differences between these two circulations were known in animals, the performance of the pulmonary circulation in normal and abnormal states in man was not clearly defined until technics became available which permitted direct measurements of pulmonary blood flow and blood pressures. In this paper some of the important features of the normal human pulmonary circulation which have become apparent during the past decade, will be reviewed as a background against which some of the patterns observed in disease may be projected.

The pulmonary circulation could logically be defined from an anatomic point of view as including all the structures from the pulmonary artery through the pulmonary veins. However, dynamically one must add the right ventricle, which in large measure controls the pulmonary blood flow, and the left atrium because the latter influences markedly pulmonary venous outflow.

The blood flow through the pulmonary circulation in normal man is quantitatively the same as that which flows through the systemic circulation, if one disregards the small contribution of the bronchiolar circulation which adds to the systemic circulation less than 1 per cent of the total cardiac output. The pressures, however, are quite dissimilar. The mean, or dynamically effective, pressure in the pulmonary artery is about one-tenth that seen in the aorta and the pressure in the pulmonary capillaries is one-sixth that of the systemic capillaries. These facts indicate that the pulmonary circulation is a low resistance system. That it is also readily distensible is shown by the fact that the flow of blood through the pulmonary arteries can be greatly accelerated without necessarily entailing a rise in pressure in these arteries. For example, blood flow through the lungs of normal man may be increased three times above the resting level, reaching values between 8 and 11 liters per minute per square meter of body surface area, without producing pulmonary hypertension. Considered from another point of view, removal of one lung and hence doubling the flow in the remaining normal lung, does not result in pulmonary hypertension and furthermore will not do so until the blood flow through the remaining lung, which before the pneumonectomy was accustomed to receiving approximately 1.5 liters per square meter of body surface area, or one-half the cardiac output, is trebled as it may be during exercise.

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As has been mentioned, the blood flow through the greater and lesser circulations is the same and presumably the average stroke outputs of the left and right ventricles are also identical in normal man. The systemic arterial tree however, has regulatory reflex mechanisms which permit this bed to adjust to changes in left ventricular stroke output and heart rate in such a way that there may not be an overall change in arterial blood pressure. Such reflex mechanisms have not been conclusively shown to exist at least under normal circumstances in the pulmonary arterial tree, where stability of the pulmonary artery pressure in face of a changing right ventricular output is chiefly a reflection of the great capacity and distensibility of the arteries, "arterioles" and capillaries. Pharmacologic studies designed to demonstrate reflex control of the pulmonary vascular bed are still in an early stage. However, it has been suggested recently that there is some vasomotor activity in the pulmonary bed because of the finding that anoxia produces pulmonary hypertension at levels of blood flow which of themselves would be insufficient to raise pulmonary artery pressures to abnormal levels in normal man. However, the mode and site of action of anoxia upon the bed have not yet been identified, although it may be that anoxia has a topical action upon the musculature of the pulmonary vessels. This entire problem is still unresolved.

Since vasomotricity cannot be directly implicated, at least as yet, in the control of lesser circuit pressures, the level of pulmonary artery pressures is largely the resultant of a balance between pulmonary blood flow and pulmonary vascular capacity, so long as there is no interference in the pulmonary venous outflow.

Extensive destruction of the pulmonary vascular tree and hence a reduction in the capacity of the bed could presumably produce pulmonary hypertension. Indeed, actual anatomic curtailment in size of the bed by rupture and thinning of the capillaries was formerly indicted as the sole cause of such a pressure rise in patients with chronic pulmonary emphysema. The reversibility of pulmonary hypertension in these patients however, has indicated that other factors, e.g. anoxia, hypercapnia, increased blood flow and hypervolemia, must be superimposed upon anatomic lesions before severe pulmonary hypertension exists. On the other hand, the size of the pulmonary vascular bed may be diminished in a somewhat different fashion by vascular lesions which encroach upon, and hence reduce the lumen of, individual vessels. This type of pathologic lesion has been described in, and may be in part responsible for pulmonary hypertension in certain congenital malformations where pulmonary blood flow is increased, e.g. interatrial septal defect and patent ductus arteriosus.

Finally, one must consider the effects of a decreased distensibility upon pulmonary vascular pressures. The sclerotic lesions observed in the arterial tree in the congenital anomalies just discussed, not only reduce the lumen of the vessels but also may alter their elasticity. A reduction in distensibility, limiting mechanical dilatation, would favor the production of pulmonary hypertension. Extensive arterial lesions have also been described in patients with mitral stenosis. The very high pulmonary artery pressures seen in

some of these individuals, whose capillary pressure in the absence of pulmonary edema must be assumed to be considerably less than arterial, can be explained by the presence of these vascular lesions and the dynamic alterations they bring in their wake. When one is analyzing problems relating to elasticity in the pulmonary circulation, it should be stressed that the component parts, arteries, capillaries, and veins, have different elasticities and hence similar volume changes may produce quite different pressure responses in these different areas. If one superimposed upon these differing elasticities, pathologic vascular lesions in the arteries which are different from and may be more limiting than those in the capillaries, as are observed in the lungs of patients with mitral stenosis, one may expect an even greater pressure gradient between pulmonary artery and capillaries to appear. Hence alterations in the physical characteristics of the system will account for the marked pressure differential and one need not invoke a vasoconstrictor response.

It is obvious that various details relating to pulmonary blood volume have not been given attention in the previous discussion. Unfortunately there is little precise knowledge concerning this most important feature of the pulmonary circulation. Not only is there no satisfactory measurement of the total volume of blood in the lungs of man in normal or diseased states, but also the distribution of this blood volume throughout the bed has not been ascertained.

It would also be of interest to know the size of the blood reservoir, if such a pooling really exists in man, and the limits of its size, since if its bounds are exceeded, clinical and physiologic evidence of pulmonary congestion would shortly appear. Whenever the right ventricle ejects more blood than can be removed by the left heart, a condition which exists in left ventricular failure and may occur in mitral stenosis, blood of an unknown amount is trapped in the lungs. However, how much blood can be added to the pulmonary bed without inducing a pressure rise is unknown but of great importance in these conditions. Improvements in technics to measure these variables are awaited with anticipation.

The physiologic terminus of the lesser circulation is, of course, the pulmonary veins and the left atrium. Because there are no pulmonary venous valves these structures should be considered as one system, the characteristics of which are a smaller capacity and a lesser distensibility than that of the systemic veins and right atrium. From a dynamic point of view this means that small changes in volume in the left veno-atrial system result in a greater pressure change than would be encountered in the right veno-atrial system for an equivalent volume change. Furthermore, pressure variations in this short system are reflected swiftly to and through the pulmonary capillary bed because of the absence of venous valves. The lack of heavy muscular coats in the precapillary vessels, implies a relative lack of automony in these "arterioles" as compared with the arterioles of the systemic circulation, and hence pressure changes in the capillary bed will be readily discernible in the pulmonary arteries.

It has been previously mentioned that there is a considerable difference

between pulmonary capillary (5 mm. Hg.) and systemic capillary (25 mm. Hg.) hydrostatic pressures. The importance of this fact is further emphasized when one relates these pressures to the plasma oncotic pressure (30 mm. Hg.) and notes that there is a greater pressure differential between oncotic and hydrostatic pressure in the pulmonary capillary system than in the systemic capillaries. Thus, for example, when an increment of pressure of similar magnitude is added to both systemic and pulmonary capillaries, as is seen in chronic constrictive pericarditis, one may expect increasing transudation of fluid into the systemic tissues without transudation into the alveoli. This explains why in this disease, with clinical evidence of considerable systemic congestion, there is seldom, if ever, frank pulmonary edema. This margin of safety within the pulmonary capillaries also accounts for the fact that patients with left ventricular failure or mitral stenosis may have moderate pulmonary hypertension without pulmonary rales.

This brief summary of the pulmonary circulation has attempted to focus attention on the mechanisms which may be involved, singly or together, in the production of pulmonary hypertension. This circulatory disorder has been emphasized because its consequences, right ventricular failure and pulmonary edema, can be so disastrous. Although the individual mechanisms which favor hypertension have been treated separately, it is obvious that in most clinical states more than one of these is involved in producing the final physiologic status. The clinical diagnosis of pulmonary hypertension is often made without difficulty in the advanced stage. Unfortunately there are as yet no constant or reliable clinical criteria for diagnosing this hemodynamic disorder, which permit its recognition in the mild and hence more easily treated phase. It is not surprising therefore that lesser degrees of hypertension, such as occur in early left ventricular failure and pulmonary emphysema, escape clinical notice. Furthermore some of the signs attributed to hypertension, e.g. a loud pulmonic second sound, may actually be misleading as has recently been found in patients with mitral stenosis, where pulmonary hypertension diagnosed clinically on this basis was found to be absent when measured directly. In other instances, severe pulmonary hypertension was present when there was no accentuation of this sound.

In a short review it is impossible to comment adequately on all the work in progress concerning the lesser circulation and perforce some material has to be omitted. However, a word should be added here concerning one interesting area of investigation, namely the existence of anastomoses between pulmonary and bronchial circulations. Although these anastomoses have not been definitely proved in normal man they have been shown to occur in a wide variety of diseases including bronchiectasis, mitral stenosis, pneumonia, pulmonary infarcts, emphysema and certain congenital cardiac conditions. These anastomoses may occur at the venous, arterial or precapillary level in these various states. However, their functional importance in affecting gas exchange, pulmonary blood flow or pulmonary pressures is yet to be defined.

SUMMARY

Some of the physiologic and anatomic characteristics of the pulmonary circulation which are important to the understanding of disease states have been reviewed. Particular emphasis has been placed upon the mechanisms producing pulmonary hypertension.

RESUMEN

Se revisan algunos aspectos de los características anatómicas y fisiológicas de la circulación pulmonar, importantes para comprender los estados de enfermedad. Resultándose especialmente los mecanismos capaces de producir hipertensión pulmonar.

RESUME

Quelques characteristiques physiologiques et anatomiques de la circulation pulmonaire qui servent à éclairer certaines maladies, ont été presentées. On à souligner particulièrement les mechanisms qui produisent l'hypertension pulmonaire.

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Pulmonary Hypertension and Its Relation to Congenital Heart Disease*

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An authoritative discussion of the subject of pulmonary arterial hypertension has only become possible within the last few years. Before the advent of cardiac catheterization clinicians suspected the existence of pulmonary hypertension, but the inaccessibility of the pulmonary arterial tree to pressure measurement made it entirely a matter of speculation. The following clinical observations were thought to represent evidence of pulmonary hypertension: (1) Accentuation of the second sound in the pulmonic area; (2) evidence of right ventricular hypertrophy and dilatation on physical, electrocardiographic and roentgenographic examinations; (3) roentgenographic evidence of dilatation of the pulmonary artery and its branches. These findings were reinforced by demonstration at the autopsy table of increased thickness of the right ventricle and of undue arteriosclerosis of the pulmonary artery and its branches. Now it is known that these clinical findings are frequently found in pulmonary hypertension, but are by no means specific for it, as they are also seen in cases in which the pulmonary circulation is overloaded by a large left-to-right shunt with little or no elevation of the pulmonary arterial pressure. Thus, our knowledge of the frequency, extent and relationship of pulmonary arterial hypertension to other factors depends entirely on the data collected on patients who underwent cardiac catheterization.

The normal pressure in the pulmonary artery averages 25/10 mm. Hg. with a mean pressure of 15 mm. Hg. Values of 35/15 and over are usually considered to be hypertensive. However, unlike in the systemic circulation, pulmonary hypertension is seldom of major importance unless it reaches the level of twice the normal value, while in severe cases, values of four or five times the normal pressure are not uncommon. Before presenting the various factors capable of elevating pressure in the lesser circulation, one should recall some physiological differences between the two circulatory systems. Since the pressure in each arterial system depends on the cardiac output and on the peripheral resistance, and since the output of both sides is, under normal circumstances, identical, it is obvious that the resistance in the systemic circulation is about four or five times higher than in the pulmonary circulation. The high resistance within the systemic circulation is offered by the conglomeration of all the systemic arterioles which are under strict control of various nervous and humoral mechanisms. The resistance at the arteriolar level is so high that circulatory changes beyond it, at the capillary and venous levels appear negligible and cannot influence arterial flows and pressures. Thus, all forms of

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systemic hypertension have to be caused by increased resistance at the arteriolar level with the sole exception of coarctation of the aorta in which mechanical constriction of the main vessel offers part of the increased resistance. In contrast to the systemic circulation, the low resistance in the pulmonary circulation is offered partly by the pulmonary arterioles, the control of which is not yet well understood, and partly by the capillaries and the emptying factors of the pulmonary veins and the left atrium. Thus, elevation of pressure in the pulmonary circulation may be brought about at three levels: (1) Increased resistance to the emptying of the pulmonary vein into the left atrium, which operates beyond the capillaries; (2) increased resistance due to the reduction of the capillary bed, or perhaps due to abnormally high intrathoracic pressure which operates at the capillary level; (3) increased resistance at the pulmonary arteriolar level may be caused either by some unknown reactions leading to arteriolar constriction, or by intraluminar occlusion by thrombi, and perhaps, inflammatory states. For that reason, one can recognize three general causes of pulmonary hypertension which are shown in Table I along with the representative clinical conditions. In this presentation, the relationship of primary "vascular" pulmonary hypertension to congenital heart disease is discussed.

TABLE I

TYPES OF PULMONARY HYPERTENSION

A. *Cardiac ("Post-capillary"):*
   1. Left ventricular failure;
   2. Mitral stenosis;
   3. Constrictive pericarditis involving the left heart.

B. *Pulmonary:*
   "Cor pulmonale" due to pulmonary emphysema, fibrosis, pneumokoniosis; chest deformities and other intrathoracic conditions.

C. *Vascular:*
   1. Primary: Congenital or acquired pulmonary hypertension of undetermined etiology.
   2. Secondary: Acute, subacute and chronic thromboembolization of the pulmonary arterial tree.

Pulmonary arterial hypertension associated with congenital cardiac malformation falls generally into two categories: One form represents conditions in which pulmonary hypertension is a constant and necessary part of the syndrome; the other form occurs predominantly with unaltered pulmonary arterial pressure but pulmonary hypertension appears as a secondary or a complicating feature.

Pulmonary Hypertension as an Essential Feature of Congenital Cardiac Syndrome

In some entities the presence of pulmonary hypertension helps to maintain a balanced flow through the two systems. This situation occurs when

a malformation of the heart or great vessels brings about a double or bifurcated outlet from a cardiac ventricle—the pressure pump. The function of a cardiac ventricle is to pump blood into the arterial system against a resistance offered by that system. If a ventricle has two outlets, the quantity of blood entering each outlet stands in inverse proportion to the resistance offered by each outlet. Thus, it can be seen that if both the aorta and the pulmonary artery were connected with the same ventricle, and if the respective resistances of the two trunks were normal, then four-fifths of the output of the ventricle would enter the pulmonary artery and one-fifth the aorta, since the resistances stand in a ratio of five to one. In such a situation, not only the quantity of blood perfusing the systemic circulation would be inadequate, but this perfusion pressure would probably be too low and life would in all likelihood be not maintainable. This situation can be best apprehended by a simple experiment with the ordinary blood pressure manometer. In the process of taking a person's blood pressure by the indirect method, the rubber bulb represents the pump which inflates the pressure in the cuff placed around the arm to a higher level than the anticipated systolic pressure. The building up of a pressure of some 150 mm. Hg. is done simply by squeezing the bulb a few times. This "single outlet" pump can be changed into a "double outlet" pump by gradually opening the side screw controlling the valve. The open valve constitutes a low resistance outlet. A slight opening of the valve permits still the building up and maintenance of pressure in the cuff by firmer and more frequent pumping to compensate for the escaped air. When the valve is opened wider, more air escapes through the side opening than can enter the cuff and adequate pressure cannot be built up at all.

Obviously, in human pathology a situation in which a cardiac ventricle has two outlets can only exist in congenital heart disease. The following malformations are thought to represent a "double outlet ventricle": (1) trilocular heart with a single ventricle and two atria; (2) partial transposition of the arterial trunks with both the aorta and pulmonary artery originating from the right ventricle; (3) a large ventricular septal defect with or without overriding of the aorta; (4) the syndrome of patent ductus arteriosus with infantile coarctation of the aorta.

These syndromes have one thing in common: a cardiac ventricle is connected with two areas which ordinarily have different resistances. In the first case a common ventricle has two outlets—the arterial trunks; in the second case these originate from the right ventricle; in the third case the left ventricle has an additional outlet: the low-pressure right ventricle; finally, in the last syndrome the right ventricle supplies, in addition to the pulmonary circulation, the blood flow through the entire lower part of the body below the coarcted or atretic aorta. If in all these conditions the pulmonary arterial system preserved its low resistance, then this would act as a hole similar to the open valve in the blood pressure manometer, interfering with an adequate flow through the other regions. This can be prevented by one of two mechanisms: either the "hole" may be closed entirely by an elevation of pulmonary arterial resistance to make it com-

parable with systemic resistance, in which case both regions would be perfused to an equal extent; or the "hole" may be partially but effectively closed by significant narrowing of the pulmonary orifice in a manner similar to a slightly open blood pressure valve in which the cuff can still be inflated to a desired pressure with a more forceful pumping action.

Both of these protective mechanisms are known to occur in conjunction with these syndromes: pulmonary stenosis is commonly associated with any of the first three syndromes; pulmonary hypertension is found regularly in those of the first three conditions in which pulmonary stenosis is not present, and in all instances of the fourth syndrome. The presence of pulmonary hypertension is shown by the regular finding of severe arteriolar changes in the pulmonary circulation which are considered the pathologic counterpart of pulmonary hypertension during life.

Thus, one can deduce from an analysis of circulatory dynamics in these unusual malformations of the circulatory system that pulmonary hypertension or constriction of the pulmonary orifice is an essential feature necessary for the preservation of life. One can further find a confirmation of the deduction by pathological and clinical findings. The unanswered question, however, remains the origin and mechanism of hypertension of the lesser circulation. Since no direct information on this matter is as yet available, one can only present syeculative ideas. During the fetal life, the resistance in the pulmonary artery and the aorta and in the two ventricles are known to be roughly the same. During the early postnatal period the following events take place: the ductus arteriosus and foramen ovale close; the wide capillary bed of the lungs opens up coincidentally with the first breath and the discrepancy between the resistance in the two systems begins to appear with the pulmonary resistance falling and the systemic increasing until the adult ratio of four to five to one is established. In rare instances this postnatal adaptation proceeds in an abnormal manner in that the pulmonary resistance maintains itself at a high level comparable to that of the systemic resistance, presumably by a persistent pulmonary arteriolar constriction. The cause of this maladjustment is not known, and it may appear as an isolated condition or as a part of a combined congenital cardiovascular syndrome. As pointed out above, in the four syndromes under discussion, this postnatal maladjustment appears to be the rule, which suggests that there is causal relationship between the circulation in a "double outlet ventricle" and the persistently high pulmonary resistance. It is not clear what constitutes the stimulus for the failure of the reduction in the pulmonary resistance, but it is possible that this is related to the overloading of pulmonary circulation which would take place with any elevation of the systemic resistance, which in turn may lead to pulmonary arteriolar constriction and redistributed the blood more evenly.

Ventricular septal defect. Because of the frequency of this lesion and its relatively benign nature permitting survival to adult life, circulatory dynamics of it are better understood than in others. It has been estimated[1] that in a smaller ventricular septal defect, roughly 1.5 cm. in diameter

or less, the interventricular communication provides in itself sufficient resistance so that a systemic flow can be maintained even with normal pressure in the pulmonary arterial system. In such cases one deals primarily with a pure left-to-right intracardiac shunt which has no direct effect upon the pulmonary arterial pressure but with which occasionally pulmonary hypertension may coexist.

Larger defects of the ventricular septum constitute the second outlet from the left ventricle which as a "double outlet ventricle" requires pulmonary hypertension since birth. Such cases are characterized by the clinical picture of high pulmonary arterial pressure with the intracardiac shunt being of lesser importance. Therefore, systolic murmurs may be less prominent than in the smaller ventricular septal defects, the intense pulmonary congestion may not be present, and the calculation of intracardiac shunt by a cardiac catheterization study may show only modest left-to-right shunt, right-to-left shunts (Eisenmenger's complex) or mixed shunts. The frequently associated overriding position of the aorta facilitates the right-to-left direction of the shunt so that the Eisenmenger's complex presents the commonest, and the most classic type of the "double outlet ventricle". This view is based on the fact that (1) in all reported instances of the Eisenmenger complex, pulmonary arterial pressure is shown to be about equal that in the aorta, that is four to five times higher than normal; (2) such findings are shown to be present in children, so that pulmonary hypertension is a stable rather than progressive feature; (3) characteristic changes in the pulmonary arterioles indicative of pulmonary hypertension are found as a rule in such cases, even in children.

Essential Pulmonary Hypertension

In a certain number of cases pulmonary hypertension is found without an obvious cause. If a careful investigation rules out a "cardiac" or a "pulmonary" type (Table I), one can assume the "vascular" type of pulmonary hypertension. After eliminating pulmonary embolization and the previously named congenital defects as a cause of the elevation of pressure in the pulmonary system, it is customary to diagnose such a case as "essential pulmonary hypertension". It should be realized, however, that such instances can be caused by more than one mechanism. The existance of a "congenital" form of isolated pulmonary hypertension is suggested by the observations, that in many proved cases of "essential" pulmonary hypertension, disability pointing to pulmonary circulation starts early in life. Furthermore, several cases of idiopathic pulmonary vascular disease have been reported in small children. These cases probably do not represent a true congenital lesion, but rather an error in postnatal adaptation, as was explained above. As such they can be considered analogous to the persistent patency of the ductus arteriosus, which also is not a congenital but a postnatal error.

In some cases pulmonary hypertension of the essential type develops later in life. While its origin may not be detectible, one can sometimes suspect other mechanisms as being responsible for the vascular changes:

a discreet form of pulmonary embolization may be clinically entirely unrecognized but may leave the patient with a seemingly primary pulmonary hypertension. In still other cases, one can suspect the development of obliterative endarteritis of the pulmonary tree due to inflammatory factors or hypersensitivity phenomena. The difficulty in deciding which is the initiating factor lies in the fact that in longstanding disease of the pulmonary arterioles the microscopic appearance is similar regardless whether such changes are due to unknown postnatal factors, to thrombotic phenomena or to inflammatory causes.

Pulmonary Hypertension as a Complication of Some Congenital Cardiovascular Syndromes

Pulmonary hypertension associated with congenital heart disease is not limited to the syndromes enumerated above, in which it is an essential feature. It is noted on occasion in other forms of congenital heart disease, primarily in syndromes associated with a left-to-right shunt. These include the atrial septal defect, the small ventricular septal defect and the patent ductus arteriosus. In all of these, the left-to-right shunt may reach a considerable magnitude. Since this marked overloading of the pulmonary circulation, on one hand, and pulmonary hypertension, on the other hand, present a similar clinical picture, and since they occasionally occur together, a casual relationship between the two has long been suspected. It has been thought that the large pulmonary flow may lead to pulmonary arteriolar changes which in turn increase the resistance bringing about pulmonary hypertension. However, more evidence has been accumulated recently which points to the fact that such a sequence of events, occurs only occasionally, if at all.

Atrial septal defect. In defects of the atrial septum the left-to-right shunt often reaches very considerable proportions, so that the pulmonary flow may be several times larger than the systemic flow. Under normal circumstances, the pulmonary resistance is not only low but adaptable, so that such a large flow through the lungs may be accomodated without an undue elevation of pulmonary pressure. In some cases mild or moderate pulmonary hypertension can be found, especially in older individuals, which may merely indicate that the pulmonary arteriolar resistance stays at a normal level rather than decreases in proportion to the increase in pulmonary flow. It is believed that true pulmonary hypertension, i.e., that associated with an increased pulmonary resistance is not the result of longstanding overloading of the pulmonary circulation because: (1) severe pulmonary hypertension found in cases of atrial septal defect does not bear any relationship to the magnitude of the pulmonary flow; and (2) it may be demonstrated in young children and is not necessarily progressive. The incidence of severe pulmonary hypertension in cases of atrial septal defect is not definitely known, but it probably constitutes less than a quarter of the cases. Pulmonary hypertension may be associated with a reversal of the shunt through the atrial septal defect leading to cyanosis and anoxemia and is recognized as an important cause of such a compli-

cation. The cause of pulmonary hypertension as a complication of the atrial septal defect is not known. It may represent any type of the "essential" pulmonary hypertension, reported in the preceding paragraph occurring coincidentally with the atrial septal defect.

Small ventricular septal defect. Defects of the ventricular septum can be divided into several forms:[1] larger defects belong in the category in which elevated pulmonary arteriolar resistance helps maintain the systemic circulation and, as pointed out before, is assumed to be present since birth. Smaller defects are consistent with a normal pressure gradient between the two ventricles and permit a left-to-right shunt of varying magnitude. Many such cases lead to a considerable overloading of the pulmonary circulation and, like in atrial septal defect, may show a normal pulmonary arterial pressure. Since the dynamics of this form of ventricular septal defect closely resembles that of the atrial septal defect and the patent ductus arteriosus, one can deduce that here, too, occasional coexistance of pulmonary hypertension may be occasionally detected. This combination is difficult to separate from a large ventricular septal defect with an "obligatory" pulmonary hypertension, but it can be suspected in those cases where (1) pulmonary hypertension is present but is not high enough to equalize pressures between the two ventricles in systole; or (2) in cases in which pulmonary hypertension develops later in life.

Patent ductus arteriosus. The magnitude of the aorto-pulmonary blood shunt in patent ductus arteriosus depends on the size of the ductus. A large ductus arteriosus permits large shunts to flood the pulmonary circulation but the pulmonary pressures are usually normal or only slightly elevated. In a small proportion of cases, pulmonary hypertension may be present, which as in the other two syndromes discusses in this section, is in no obvious relationship to the size of the shunt.

In the syndrome of patent ductus arteriosus with pulmonary hypertension, a considerable pulmonary hypertension may be present while a large left-to-right shunt still takes place. However, when the resistance in the pulmonary circuit equals or exceeds that in the systemic circulation, a reversal of flow through the ductus occurs which leads to a characteristic anoxemia and cyanosis demonstrable differentially in the lower part of the body. Pulmonary hypertension in cases of patent ductus arteriosus may be present since childhood, in fact, chronic cyanosis due to a direction reversal of the shunt in the ductus has on occasion been noted since birth. This is the strongest available evidence of the "congenital" nature of pulmonary hypertension in this syndrome. It is even possible, that an error of the neonatal adaptation leaving a persistently high pulmonary resistance may interfere with the closure of the ductus, which thus could be considered a secondary feature of "essential" pulmonary hypertension since birth.

Clinically, the syndrome of pulmonary hypertension with patency of the ductus arteriosus presents a fairly characteristic picture which can be suspected with the aid of simple clinical methods, and proved without difficulty by cardiac catheterization. In such cases the diastolic part of

the continuous "ductus" murmur is obliterated, right ventricular enlargement can be demonstrated and an undue prominence of the pulmonary artery and its branches is noted. In "reverse ductus," arterial oxygen saturation in arteries of the upper extremity may be normal, but is always reduced in samples obtained from the femoral artery.

SUMMARY

Of the various types of pulmonary hypertension the primary, "vascular" form is frequently associated with congenital heart disease. Primary pulmonary hypertension can usually be demonstrated in children and is presumed to be related to a maladjustment of the pulmonary circulation during the postnatal adaptive period. In such cases equal resistances within the pulmonary and systemic circuits, which are essential in the fetal circulation, persists into postnatal life. This form of severe pulmonary hypertension appears in three clinical types: (1) a "primary" form in which it is not associated with any other cardiac malformation; (2) a type in which the persistence of the fetal-like equalization of pulmonary and systemic resistance exerts an important protective function by preventing an unequal distribution of the blood and, (3) the type in which pulmonary hypertension is found occasionally in association with congenital syndromes causing a left-to-right shunt, which ordinarily show normal pulmonary arterial pressures. In the second type a causal relationship between the cardiac malformation and the persistence of high pulmonary resistance has not been demonstrated but appears highly probable. In the third type pulmonary hypertension is probably a coincidental complication of the cardiac defect as it appears to be unrelated to the magnitude of the shunt and to the large pulmonary blod flow.

RESUMEN

De las formas varias de hipertensión pulmonar, la primaria o forma "vascular," se asocia frecuentemente con una enfermedad congénita del corazón. La hipertensión primaria pulmonar, puede demostrarse en niños generalmente, y se presume que se debe a la falta de adaptación de la circulación pulmonar durante el período de ajuste postnatal. En tales casos hay resistencias iguales dentro de la circulación pulmonar y en la general, lo cual es esencial en la circulación fetal y que persiste en la vida postnatal. Esta forma de hipertensión pulmonar severa, aparece en tres tipos: (1) una forma "primaria" que no está asociada con ninguna otra malformación cardiaca; (2) un tipo en el que hay persistencia de la igualdad de las resistencias pulmonar y general como en el feto y en la que esa persistencia ejerce una función protectora importante para evitar una distribución desigual de la sangre y la (3) que es el tipo en el que hipertensión pulmonar se encuentra ocasionalmente en asociación por síndromes congénitos que causan un "shunt" o paso de izquierda-derecha y que ordinariamente muestra presiones de las arterias pulmonares normales.

En el segundo tipo no se ha demostrado una relación causal entre la malformación cardiaca y la persistencia de elevada resistencia pulmonar, pero es muy probable que exista.

En el tercer tipo la hipertensión pulmonar, es probablemente una coincidencia como complicación del defecto cardiaco puesto que parece sin relación con el paso o "shunt" ni con el gran flujo de sangre pulmonar.

RESUME

Parmi les différentes formes d'hypertension pulmonaire, le type primitif ou "vasculaire" est fréquemment associé à une cardiopathie congénitale. L'hypertension pulmonaire primitive peut habituellement être mise en évidence chez les enfants. Elle parait devoir être attribuée à une mauvaise disposition de la circulation pulmonaire au cours de la période d'adaptation qui suit immédiatement la naissance.

Dans de tels cas, l'égalité des résistances de la circulation pulmonaire et de la circulation générale, qui joue un rôle capital dans la circulation foetale persiste après la naissance. Cette forme d'hypertension pulmonaire grave peut se présenter sous trois types cliniques:

1) La "forme primaire" qui ne se trouve associée à aucune autre malformation cardiaque.

2) La forme dans laquelle la persistance de l'égalité des résistances entre le système pulmonaire et le système général comparable à ce qui se passe dans la vie foetale, constitute une protection importante et évite une inégalité de distribution sanguine.

3) La forme dans laquelle l'hypertension pulmonaire est découverte par hasard, associée à des syndromes congénitaux, qui détermine un "shunt" de gauche à droite, qui s'accompagne habituellement d'une pression normale dans l'artère pulmonaire.

Dans la seconde forme, on n'a pas pu démontrer qu'il y ait une relation de cause à effet entre la malformation cardiaque et la présence d'une résistance pulmonaire élevée mais cette relation parait vraiment probable. Dans la troisième forme, l'hypertension de l'artère pulmonaire est vraisemblablement une complication fortuite de la défaillance cardiaque. Elle semble ne pas avoir de relation avec l'importance du shunt, et l'importance du débit pulmonaire.

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An Analytic Review of Excisional Surgery for Pulmonary Tuberculosis

(Sea View Hospital — 1944-1952)

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In recent years the results of Excisional Surgery have been well crystalized in the papers of Bailey, Overholt, Murphy, Sweet, Crafoord, Clagett[1-6] and others. Therefore, it is not the purpose of this article to prove or disprove the case for as well accepted a procedure as pulmonary excision, but rather to present an accurate statistical appraisal of the results of excisional surgery for pulmonary tuberculosis at Sea View Hospital from 1944 to February, 1952. A further attempt will be made to discuss fully the results and problems encountered in an adequate follow-up and rehabilitation of the excisional patient.

There have been a total of 512 excisions in 487 patients, performed by 21 visiting and resident surgeons during this eight year period. All cases, with the exception of the first 24, have had the benefit of streptomycin during surgery and all operations were done in the face-down position.

The ages ranged from 2 to 63 years, with an average age of 31.0 years. There were 182 males (37 per cent) and 305 females (63 per cent) in this series.

AGE DISTRIBUTION

0-9	*10-19*	*20-29*	*30-39*	*40-49*	*50 & Over*
4 (0.8%)	54 (11.1%)	186 (38.2%)	137 (27.9%)	76 (15.6%)	30 (6.2%)

RACIAL DISTRIBUTION

	No.	Pct.
Negro	243	(49.9)
White	138	(28.3)
Spanish-American	100	(20.5)
Chinese	6	(1.3)

Indications:

At Sea View Hospital the indications for excisional surgery follow the pattern set forth in most clinics throughout the country. However, this institution is a cauldron into which far advanced pulmonary tuberculous

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patients are deposited. With very few exceptions, all pre-operative cases have had positive sputa. The indications, in the main, are as follows:

INDICATIONS FOR EXCISIONAL SURGERY FOR PULMONARY TUBERCULOSIS AT SEA VIEW HOSPITAL

I. *Collapse Therapy Failure*
   1. Pneumothorax failure.
   2. (Pneumoperitoneum failure).
   3. Extra pleural pneumothorax failure.
   4. Thoracoplasty failure.

II. *Anticipated Collapse Therapy Failure*
   A. Predominantly pulmonary:
      1. Destroyed lobe of lung.
      2. Giant cavity.
      3. Rapidly progressive disease.
      4. Unfavorably located cavitary disease.
      5. Persistent cavitary disease uncontrolled by medical management.
      6. Tuberculoma.
   B. Predominantly bronchial:
      1. Bronchostenosis.
      2. Tuberculous bronchiectasis.
   C. Predominantly pleural:
      1. Tuberculous empyema with destroyed lobe of lung.
      2. B.P.F. and empyema with destroyed lobe of lung.

III. *Emergency Resection*
   1. Uncontrollable hemoptysis.
   2. Acute cavity rupture or anticipated cavity rupture.

IV. *Resectional Surgical Failures*
   (i.e. Completion lobectomy or pneumonectomy for uncontrolled disease [residual cavitary disease] or broncho pleural fistula).

Table I will reveal a breakdown of the excisional cases by year.

TABLE I
NUMBER OF PATIENTS FOLLOWED

Year	Total Ops. Performed	Attending Clinic	Hosp'd.	Priv. Phys. or Clinic	Totals	Dec'd.	Not Followed
1944	2	1	0	1	2	0	0
1945	1	1	0	0	1	0	0
1946	19	7	0	0	7	9	3
1947	57	34	3	5	42	10	5
1948	107	61	2	9	72	27	8
1949	111	50	5	11	66	22	23
1950	77	25	10	11	46	13	18
1951	97	26	51	3	80	15	2
1952	16	0	15	0	15	1	0
TOTALS	487	205	86	40	331	97	59

TABLE III: DISTRIBUTION — 512 EXCISIONS IN 487 PATIENTS

		Deaths No. Pct.	B.P.Fs. No. Pct.	B.P.Fs. Closed	Empyema	Esophageal Fistula	Chylo Thorax	Wound Infection
PNEUMONECTOMIES:								
Right	148	34 (23.1)	32 (21.5)	11	2	3	1	6
Left	185	34 (18.7)	15 (8.1)	4	6	0	0	12
TOTALS	333	68 (20.7)	47 (14.1)	15	8	3	1	18
LOBECTOMIES:								
RUL	74							
RUL and RML	9							
	83	16 (19.3)	21 (25.3)	8	3	-	-	2
RLL	6							
RUL and RM L	9							
	15*	4 (33.3)	3 (25.0)	2	1	-	-	1
LUL	43	5 (11.6)	7 (16.3)	3	2	-	-	1
LLL	9†	1 (16.6)	0					
TOTALS	150**	26 (17.3)	31 (21.5)	13	6	-	-	4
SEGMENTAL RESECTIONS:								
	29††	3 (10.7)	4 (14.3)	2	0	-	-	1
Total Excisions	512	97 (19.9)	82 (16.2)	30 (36.6%)	14 (2.3%)	3	1	23 (4.5%)

*3 completion pneumonectomies for B.P.Fs.

†3 completion pneumonectomies for B.P.Fs.

**(1) Six excisions—completion pneumonectomies for B.P.Fs.
(2) Ten completion pneumonectomies for residual cavitary disease (lobectomy failure).
(3) Two bilateral excisions (lobectomies).
(4) In 19 lobectomies the superior segment of lower lobes also excised.

††(1) One completion lobectomy (lingula) for B.P.F.
(2) Three bilateral excisions (lobectomy with contra-lateral segmental resection).
(3) Three operated for residual cavitary disease with segmental resection.

Extra-Pulmonary Diseases—Tuberculous:

In indicated cases, patients with extra-pulmonary foci had surgical treatment for these foci either before or after pulmonary resection. Neither during nor after pulmonary surgery did these extra-pulmonary foci create any specific hazard.

1. Laryngeal tuberculosis	19
2. Osseous tuberculosis	12
3. Tuberculous otitis	7
4. Tuberculous mastoiditis	5
5. Rectal tuberculosis	8
6. Tuberculous lymphadinitis	6
7. Renal tuberculosis	5
8. Tuberculous epididymitis	5
9. G.I. tuberculosis	4
10. Occular tuberculosis	3
11. Tuberculoma brain (x-ray)	1

Extra-Pulmonary Diseases—Non-Tuberculous:

Here, too, the extra-pulmonary disease did not complicate excision nor did the pulmonary tuberculosis flare up as a result of excision with the following diseased processes:

1. Diabetes mellitus	19
2. Asthma	6
3. Psychosis	5
4. Hydronephrosis	2
5. Polycystic disease, kidney (excised)	1
6. Mental defective	2
7. Rheumatic heart disease	4
8. Arteriosclerotic heart disease with hypertension	2
9. Amyloid disease	5
10. Giant cell sarcoma (tibia amputated)	1
11. Epilepsy	1
12. Syphilis	32

On occasions, the asthmatic has posed an additional post-operative problem, for during an asthmatic episode it seemed that it was more difficult to obtain and maintain a clear or cleared tracheo-bronchial tree. Fortunately, all cases responded to the customary management.

In the majority of the 19 cases with diabetes mellitus, subsequent to surgery their diabetic status improved markedly. Insulin requirements were either decreased or even eliminated. Five cases were controlled by diet alone, post-operatively. However, in a few instances post-operative management was difficult but, with careful medical cooperation, these patients responded well. When compared with the non-diabetic, there has been little recognizable difference, percentage-wise, in number or kind of complications.

In these 512 excisions performed on 487 patients, there are 97 known deaths from all causes, representing a 19.9 per cent mortality rate. Eighty two (16.2 per cent) broncho-pleural fistulae were encountered, many of

whom developed sinuses and empyemata. Fourteen (2.3 per cent) patients developed empyema without the presence of a broncho-pleural fistula. Twenty three (4.5 per cent) patients had post-operative wound infections or chest wall sinuses. Of these, all except three have healed and closed. Five developed respiratory difficulties and are more accurately termed cardio-respiratory "cripples". These five patients, who had pneumonectomies for destroyed lungs, were considered as "poor risks" prior to surgery, yet no other form of therapy offered any possible success. Five who received bilateral excisional surgery are well, being symptom-free, with negative sputa. Twenty three individuals, at the time of surgery, carried a contra-lateral therapeutic pneumothorax. Of these, two have positive sputa; one has contra-lateral disease; two died as a result of traumatic pneumothorax. Thirty disclosed a progression of their disease or an exacerbation, in spite of the administration of streptomycin before and after surgery.* Fifteen of these patients were subsequently controlled with pneumothorax, medical management or further surgery. With no attempt to over-emphasize excisional surgery, it can be said that there have been few spreads, keeping in mind particularly the fact that many of these patients had contra-lateral disease at the time of surgery.

Of the 512 excisions (Table III) there were 333 pneumonectomies, 150 lobectomies and 29 segmental resections. There were 68 (20.7 per cent) deaths of the 333 pneumonectomies with 47 (14.1 per cent) B.P.F.'s. Of note, there were more deaths following right pneumonectomy (23.1 per cent) than left pneumonectomy (18.7 per cent) but, of particular interest, far more broncho-pleural fistulae occurred on the right, an almost three to one, right versus left B.P.F. ratio (21.5 per cent right; 8.1 per cent left).

The mortality rate for lobectomies was less than for pneumonectomies (17.8 per cent). Again, the death rate, as noted in Table III, was greater for right lobectomy than left, as was the incidence of B.P.Fs.

The death rate for segmental resections was still lower (10.7 per cent) but the B.P.Fs. rate (14.3 per cent) was almost the same as for pneumonectomies (14.1 per cent).

It will also be noted that there were 25 patients operated upon a second time. Five were bilateral excisions, all of whom, at the present time, are doing well. There were two bilateral upper lobectomies and the other three bilateral excisions represented lobectomy on one side with contra-lateral segmental resection. Sixteen completion pneumonectomies were performed, six of which were for B.P.Fs.; five of these have remained closed. Another, a completion lobectomy (lingula), rendered adequate control of a B.P.F. of the left true upper lobe bronchus. Three patients had residual cavitary disease in segments requiring subsequent re-operation with segmental excision.

Mortality Evaluation:

There was an overall 97 (19.9 per cent) death rate in this series. The operative mortality is 15.4 per cent broken down as follows:

*Eleven of the remainder have died; four are not controlled.

I. OPERATIVE DEATHS IN THE OPERATING ROOM		**8 (1.6%)**
Hemorrhage	3	
Cardiac arrest	3	
Shock	2	
II. IMMEDIATE POST OPERATIVE DEATHS (to 72 hrs.)		**19 (3.9%)**
Due to hemorrhage and shock	9	
Pulmonary edema	3	
Heart failure	3	
Pulmonary embolus	1	
Cavitary hemorrhage (contralateral lung)	1	
Pulmonary insufficiency (contralateral pneumothorax)	1	
Tuberculous bronchopneumonia (?)	1	
III. EARLY OPERATIVE DEATHS (72 hrs. to 2 mos.)		**21 (4.3%)**
B.P.F. and empyema	8	
Pulmonary edema	3	
Post-excisional thoracoplasty	3	
Pulmonary insufficiency	2	
Spontaneous contralateral pneumothorax	1	
Bronchopneumonia	1	
Spread	1	
Completion pneumonectomy (O.R.)	1	
Amyloid disease (pre-operative)	1	
IV. LATE OPERATIVE DEATHS (over 2 mos.)		**27 (5.5%)**
B.P.F. and empyema	23	
(a) 2 with esophageal fistula		
(b) 7 had amyloid degeneration		
Cor pulmonale	4	
V. PULMONARY TUBERCULOSIS (7 mos. to 6 yrs. post-op.)		**11 (2.3%)**
(a) Principally progressive disease and/or exacerbation		
(b) 2 purportedly spreads		
VI. PULMONARY NON-TUBERCULOUS		**2 (0.4%)**
(a) Pneumococcic pneumonia	1	
(b) Bronchopneumonia (4 yrs. post-op.)	1	
VII. EXTRANEOUS CAUSES		**9 (1.9%)**
Unknown	5	
Bowel obstruction	1	
Cerebral vascular accident	1	
Cocaine sensitivity (bronchoscopy)	1	
Perforated gall bladder	1	

Sex Distribution:

The death rate among males of 24.2 per cent and for females 17.4 per cent represents about a 4:3 ratio. It is difficult to offer an explanation but the following factors may render some reasonable causes: firstly, the reluctance of males to accept surgery as readily as the women; secondly, they fall in a slightly older age group, and, thirdly, many of the men in this group are or have been chronic alcoholics.

Racial Distribution — Deaths:

	No.	Pct.
Negro	53	(21.8)
White	28	(20.3)
Spanish-American	14	(14.0)
Chinese	2	(33.3)

With the exception of the Spanish-American group there appears to be no corelation to race. The 14.0 per cent death rate, though, may be due to a somewhat younger average age group.

Deaths — Ages:

It does appear that the increase of death roughly parallels the increasing age decades.

Average Age: 34.0 years.

0-9	*10-19*	*20-29*	*30-39*	*40-49*	*50 and over*
0	9 (16.7%)	31 (16.6%)	25 (18.2%)	22 (29.0%)	10 (33.3%)

Fistula Evaluation:

Broncho-pleural fistula and empyema, usually associated complications, were the largest complicating group. In addition, they accounted for the majority of deaths. It is not within the scope of this discussion to enter into a controversy as to the pathogeneses of fistulae, whether they arise from a collection of pus outside the bronchus, which burrows into the bronchial lumen, or whether they are the result of the endo-bronchial disease progressing peripherally, or whether they result from rigid anatomy. There were 82 or 16.2 per cent proved broncho-pleural fistulae. The diagnosis is established clinically, bronchoscopically or radiographically, and, on occasion, at the time of subsequent surgery. The instillation of methylene blue has been used with varying success to correlate these other findings. Again, there is an apparent age correlation to the incidence of broncho-pleural fistula, as noted above in the mortality statistics.

0-9	*10-19*	*20-29*	*30-39*	*40-49*	*50 and over*
0	10 (18.5%)	21 (11.5%)	24 (17.5%)	18 (23.7%)	9 (30.0%)

Of the 82 fistulae, 31 (37.8 per cent) died with associated empyema; eight with amyloid degeneration, general toxicity and debilitation. Thirty (36.6 per cent) have had the broncho-pleural fistula subsequently closed by surgical intervention, i.e.:

12 closed by bronchoplasty and thoracoplasty.
12 closed by bronchoplasty and/or thoracoplasty. administered.
5 controlled by completion of pneumonectomy.
1 by completion of lobectomy (lingula).
21 (25.6 per cent) are still open and under treatment, nine of whom are hospitalized.

Sex Distribution: Male, 41 (22.5 per cent); Female, 41 (13.4 per cent).

Racial Distribution:

	No.	Pct.
Negro	39	(16.0)
White	30	(21.7)
Spanish-American	10	(10.0)
Chinese	3	(50.0)

The difference observed above in the incidence of bronchial fistulae as to sex (almost 2:1 male; female ratio) and race probably could be explained, if possible, as in the instance of the mortalities. In either event, the difference is great enough to be significant in this group.

In reviewing these cases of excisional surgery, certain interesting problems are realized:

1) Do diabetics tolerate this procedure, and do they develop complications more frequently than the non-diabetics?
2) How well do patients 50 years and older tolerate this procedure?
3) Will a female patient be able to carry a pregnancy with safety from relapse after a siege of tuberculosis and excisional surgery?
4) What is the "cure" rate?
5) Finally, can the so-called "cured" patient be rehabilitated and to what extent?

An attempt will be made to answer these questions by elaborating on the results in these categories at Sea View Hospital.

Results in Diabetes Mellitus:

Many writers believe that the diabetic is more prone to develop tuberculosis than the non-diabetic. In Ferrara's[7] recent evaluation of the tuberculous diabetic he noted that tuberculosis is three times as prevalent among diabetics as in the general population. This was shown at autopsy by Root and Bloor[8] and they also pointed out that the rather marked decline in the mortality rate of the tuberculous patient, in recent years, was a trend not comparably noted in the tuberculous diabetics.

Nineteen diabetics between the ages of 18 and 61 years were operated on for pulmonary tuberculosis at Sea View Hospital. The average age was 44.3 years. There were nine females and 10 males.

The complications are as follows:

	No.	Pct.
Bronchopleural fistulae	4	(21)
Deaths	4	(21)
Quadriplegia (thrombosis vert. ar.)	1	
Respiratory "cripple"	1	

These results compare favorably with the 40-49 age group as noted below:

40-49 age group:	B.P.Fs.	23.7%	Diabetics:	B.P.Fs.	21%
	Deaths	29.0%		Deaths	21%

As suggested by Root in Joslin's text, "Treatment of Diabetes Mellitus,"

excisional surgery may be that ray of hope in controlling the diabetics' pulmonary tuberculosis.

Results in Patients 50 Years and Over:

Thirty patients 50 years or over were operated upon. Their ages ranged from 50 to 63, with an average age of 53.9. The overall death rate was 33.3 per cent and the broncho-pleural fistula rate, 30 per cent.

A breakdown of the operative procedure and results in this group follows:

PNEUMONECTOMIES — 20:			6 B.P.F. (30%)
Dead		6 (30%)	2 dead 3 now closed 1 living, with empyema
Living		14 (70%)	
Living and well	11		
Contralat. dis.	1		
Resp. cripple	1		
B.P.F. and empyema	1		
LOBECTOMIES — 10:			3 B.P.F. (30%)
Dead		4 (40%)	1 dead 1 now closed 1 living, with empyema
Living		6 (60%)	
Living and well	5		
B.P.F. and empyema	1		

Pregnancy in Excisional Surgery:

One may ask, does gestation, parturition or the post-partum period influence the patient's post-excisional course? Should these patients avoid pregnancy? Or, should pregnancy be interrupted? It is believed that the extent and type of the disease in the remaining pulmonary tissue are the factors which determine the subsequent course. The consideration of these factors influenced the original decision for surgery. Apparently they were not considered disturbing burdens. Therefore, it is believed that, generally, the pregnancy should not be terminated.

To date, the follow-up study reveals that 37 excisional cases have had 41 pregnancies, four patients have had two pregnancies during or since their excisions. The ages ranged between 19 and 39 years. The average age was 25.9. Twenty nine had far advanced pulmonary tuberculosis and eight were moderately advanced. All pregnancies have occurred in the past two and one-half years.

TYPE OF SURGERY:

24 Pneumonectomies (14 left); 4 with contralateral pneumothorax.
(10 right); 1 with B.P.F. (healed).

9 Lobectomies (4 RUL — 1 with RML) [1 patient had bilateral excision].
(6 LUL — 2 with S.S.) — 1 RUL with B.P.F. (healed).
1 with contralateral pneumothorax.

4 Segmental Resections.

Deliveries:
- 6 caesarian sections
- 4 awaiting delivery
- 19 spontaneous deliveries
- 4 aborted
- 1 difficult forceps
- (others unknown).

Terms:
- 5 prematures (2 died)
- 19 full term
- 1 set o f twins
- (others unknown).

There were three pregnancies during surgery:
- 1 at 4 mos. to term (baby and mother well)
- 1 at 6 wks. (awaiting delivery — in 6th mo.)
- 1 at 6 wks. aborted 48 hrs. post-op.

Follow-up:
- 32 followed in O.P.D.
- 1 convalescing excisional surgery (rehabilitation) 6 mos. pregnant — (signed out)
- 3 not followed
- 1 dead due to exacerbation of pulmonary tuberculosis 6 yrs. post-op.

Thirty six of these mothers continue in good health, except for one just noted, who was in the hospital with an exacerbation of bilateral disease following pregnancy and recently died.

No attempt was made to control the incidence of pregnancies. However, in the light of these statistics, it is felt that pregnant patients, who have had excisional surgery for pulmonary tuberculosis as control measures for their disease, fare exceptionally well.

Operative Results:

The Sea View Hospital post-excisional follow-up clinic was established in November, 1949. Many difficulties were encountered in tracing these "lost" cases and it is, therefore, gratifying to note that 331 of 390 known living patients are being followed. They constitute an 85 per cent doctor-to-patient contact. Fifty nine (15 per cent) have been lost to follow-up but, gradually, this percentage is being decreased, particularly with the aid of the New York City Department of Health and other health agencies.

The breakdown is as follows:

1. Followed in the O.P.D.	205	
2. Followed by private physicians or other clinics	40	
3. Hospitalized	86	
Total Followed	331	(85%)
Lost to Follow-up	59	(15%)

Of the 86 hospitalized patients, 53 are awaiting discharge, in good condition. It may be added that they are now on routine post-operative rehabilitation. The remaining 33 have either a surgical complication or active pulmonary tuberculosis:

1. Complications:
   a. Broncho-pleural fistula 9
   b. Empyema 7
   c. Wound infections 2
2. Active pulmonary tuberculosis 15 (of these, seven have positive sputa)

Rehabilitation:

The knowledge that these patients can be returned to a useful position in society is most gratifying and stimulating.

Of the 208 patients seen in the clinic 121 (58.8 per cent) are on full time activity. Thirteen (6.0 per cent) were readmitted to the hospital for unstable disease or for further evaluation. Three (1.5 per cent) have died (these were patients, who at one time or another, were seen at the follow-up clinic). A more detailed analysis of these patients' activities will be found in Tables VI, VII and VIII.

Full time activity is regarded as either full time employment on the outside, full time educational pursuits or full time household duties. An eight-hour day is considered as full time employment or work tolerance.

TABLE V

GENERAL STATISTICS

Total Number of Patients—208*

Female — 136 Male — 72

Operations:

PNEUMONECTOMY		LOBECTOMY		TOTAL
Male	Female	Male	Female	
49	104	23	32	208

Race and Sex:

	White		Colored		Puerto Rican		Yellow		TOTAL
	M	F	M	F	M	F	M	F	
	28	21	24	78	17	37	3	0	208
TOTALS	49		102		54		3		

Age of Patients:

Years	Male	Female	TOTALS
10-20	3	23	26
21-30	28	71	99
31-40	24	32	56
41-50	13	8	21
51-60	4	2	6
GRAND TOTALS	72	136	208

*Three patients died during follow-up.

TABLE VI

BREAKDOWN OF PATIENT ACTIVITIES BY SEX AND SOURCE OF INCOME

				(Source of Income)		
	Female	Male	TOTAL	Self	Family	Public Assist.
I. *Full time, Normal Activity:*						
(a) Employment	17	16	33	32	1	
(b) Housework	66	1	67		29	39
(c) School of Training	3	4	7		4	3
(d) Unemployed Employables (8 hrs. tolerance)	3	11	14		7	9
II. *Part Time Activity:*						
(a) Employment	1	1	2	1	1	1
(b) Training	4	2	6	1	2	4
(c) School	2	2	4		1	3
(d) Housework	18	5	23	1	10	14
III. *Miscellaneous:*						
(a) Not Employable:						
1. Medical Reasons	10	19	29		10	19
2. Psycho. Reasons	1	1	2		1	1
(b) Pregnant	5		5		2	3
(c) Hospitalized	4	9	13			
(d) Deceased	2	1	3			
GRAND TOTALS	136	72	208	35	68	96

TABLE VII

BREAKDOWN OF PATIENT ACTIVITIES BY OPERATION AND PER CENT

	Pneumonectomies	Segmentals and Lobectomies	TOTAL	Per cent
I. *Full Time, Normal Activity:*				
(a) Employment	24	9	33	15.9
(b) Housework	53	14	67	32.3
(c) School	5	2	7	3.4
(d) Unemployed Employables (8 hrs. tolerance)	10	4	14	6.8
TOTALS	92	29	121	58.24

TABLE VII (Continued)

	Pneumonectomies	Segmentals and Lobectomies	TOTAL	Per cent
II. *Part Time Activity:*				
(a) Employment	2	0	2	.96
(b) Training	1	5	6	2.88
(c) School	4	0	4	1.92
(d) Housework	20	3	23	11.04
TOTALS	27	8	35	16.80
III. *Miscellaneous:*				
(a) Not Employable:				
1. Medical Reasons	19	10	29	13.92*
2. Psycho. Reasons	1	1	2	.96
(b) Pregnant	3	2	5	2.40
(c) Hospitalized	8	5	13	6.24**
(d) Deceased	3	0	3	1.44†
TOTALS	34	18	52	24.96

*13 by reason of recency of discharge from hospital. It is assumed that this group will reflect the same range of activity as the figures on the group as a whole indicate.
4 by reason of x-rays (unstable lesion).
2 retired.
10 physical complaints.

**6 readmitted for positive sputum.
6 readmitted because of unstable lesions revealed on x-ray.
1 for draining sinus.

†3 3 (1 male; 2 females) pneumonectomies. Causes of death: one cor pulmonale; one exacerbation of tuberculosis lesion on contralateral side; one perforated gall bladder.

TABLE VIII

TYPES OF OCCUPATIONS

OCCUPATION	NO. OF PATIENTS Male	Female	TOTALS
Sewing Machine Operator		7	7
Clerk	2	2	4
Building Superintendent	2		2
Secretary		1	1
Machinist	1		1
Machine Repairman	1		1
Machine Stamper	1		1
Foreman Supervisor	1		1

TABLE VIII (Continued)

OCCUPATION	NO. OF PATIENTS Male	Female	TOTALS
Clerical Supervisor	1		1
Accountant	1		1
Dentist	1		1
Hand Bag Cementer	1		1
Wire Tester		1	1
Waitress		1	1
Salesman	1		1
Candy Packer		1	1
Mechanical Optician	1		1
Power Press Operator	1	1	2
Messenger	1		1
Wrapper		1	1
Bar Maid		1	1
Film Collator		1	1
TOTALS	16	17	33*

*11 returned to former occupations.
12 to new occupations through training by community Agencies.
10 to new occupations after counselling.

The type of employment varies. There are bar-maids, waitresses, trade-school student, university student, power-press operator, house-to-house canvassor, salesman, accountant, machinist and many sedentary occupations. Eleven patients have been returned to their former occupations. Thirty five are on part time activities. Fifty two, as noted, are not employable. The majority, or 39, are not employed for medical reasons, i.e., due to too recent discharge from the hospital.

Conclusions:

In the evaluation of these 512 excisions in 487 patients it is realized that, in many instances, it is too early to draw definitive conclusions because of so short a follow-up period. However, bringing the 390 living patients under closer scrutiny the following results are observed:

Deaths (all causes)— 97 (19.9%)
Living* —390 (80.1%)
TOTAL* —487 (100%)

Lost to follow-up— 59 (15%)
Followed —331 (85%)

298 (90%) negative and well.
18 (5.5%) surgical complications.
15 (4.5%) active pulmonary tuberculosis, 7 with positive sputa.

*Note page 271, "Operative Results".

The apparent age relationship of increasing death and fistula incidence in the aging patient has been previously discussed. At the present time we are in the process of evaluating the importance of the condition of the bronchus and its surgical treatment, intrapleural and extrapleural dissection planes and the value of thoracoplasty in relationship to the incidence of post-operative complications, with special reference to fistulae and empyemata.

With these gratifying overall results and the excellent recovery from pulmonary tuberculosis of pregnant, diabetic and even elderly patients, excisional surgery has emerged from its infancy.

At present, with indications more clearly defined and newer surgical and anesthetic technics developed, results will continue to improve. Thus, the tuberculous patient is rehabilitated and restored to a useful life in society.

SUMMARY

1) Results of 512 pulmonary excisions in 487 patients at Sea View Hospital (1944 to February, 1952) are presented and analyzed with the indications discussed.

2) The complications of 333 pneumonectomies, 150 lobectomies and 29 segmental excisions are presented with percentage evaluation of 97 deaths and 82 broncho-pleural fistulae.

3) The results of 30 patients over 50 years of age, 19 patients with diabetes mellitus and 37 patients with 41 pregnancies, are clearly evaluated.

4) The ultimate follow-up of 390 living patients is considered with 90 per cent negative and well. Two hundred and five attend the clinic, 40 are followed by private physicians and other clinics, 86 are hospitalized and 59 are at present lost to the follow-up clinic.

5) The problem of rehabilitation and full-time activity of 208* patients is discussed, as well as a presentation of some of their activities, with 121 on full time activity.

*Three of these have died during follow-up.

RESUMEN

1) Se presentan los resultados de 512 resecciones pulmonares en 487 enfermos del Sea View Hospital (1944 a Febrero de 1952) y se analizan así como se discuten las indicaciones.

2) Se da cuenta de las complicaciones en 333 neumonectomías, 150 lobectomías y 29 calculado para resecciones segmentarias con un porcentage de 97 defunciones y 82 fístulas broncopleurales.

3) Se evalúan con claridad los resultados en 30 enfermos mayores de 50 años; 19 con diabetes, y 37 enfermos con 41 embarazos.

4) El seguimiento de los enfermos hasta ahora, da de 390 vivos con 90 por ciento negativos y bien. Doscientos cinco asisten a la clínica, 40 son observados por sus médicos o por otras clínicas; 86 están hospitalizados y 59 se han perdido de vista.

5) El problema de la rehabilitación y de la actividad completa de 208

enfermos, se discute así como se presentan algunas de las actividades que tienen, siendo 121 los que tienen plena actividad de trabajo.

RESUME

1) Les auteurs présentent, analysent et discutent les indications de 512 exérèses pulmonaires pratiquées chez 487 malades au Sea View Hospital, entre 1944 et février 1952.

2) Ils rapportent les complications survenues au cours de 333 pneumonectomies, 150 lobectomies, et 29 exérèses segmentaires. Le pourcentage de décès fut de 97 et il y eut 82 cas de fistules broncho-pleurales.

3) Ils évaluent avec précision les résultats obtenus chez 30 malades âgés de plus de 50 ans, 19 malades atteints de diabète sucré, et 37 malades qui devinrent enceintes une ou plusieurs fois (41 grossesses).

4) Le dernier bilan de 390 malades encore vivants révèle 90% d'individus en bon état et avec expectoration négative. 205 furent examinés à la clinique, 40 sont suivis par des médecins privés, ou par d'autres cliniques, 86 sont actuellement hospitalisés, et 59 n'ont pu, pour le moment, être retrouvés.

5) Les auteurs discutent le problème de la réadaptation et de l'activité à temps complet pour 208 malades. Ils exposent quelques-unes de leurs occupations, 121 malades travaillant à temps complet.

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Inhalation of Dihydrostreptomycin Dust in the Treatment of Diseases of the Respiratory Tract*

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Antibiotics given in the form of dry dust aerosols, offer a simple therapeutic approach to many of the common diseases of the respiratory tract. The favorable reports in the recent literature on the inhalation of therapeutic agents (particularly penicillin) both by dry dust and moist aerosolization have instigated the present clinical investigation of the inhalation of dry dust dihydrostreptomycin sulfate in the treatment of pulmonary disease.

The investigation had four objectives:

1) To determine the effectiveness of dihydrostreptomycin dust therapy upon the bacterial flora of the respiratory tract.
2) By means of blood level assays, to show the absorbability of dihydrostreptomycin sulfate into the circulatory system—to determine whether its action is purely topical or systemic or both.
3) To note the frequency of allergic responses and the extent of untoward reactions of this drug when inhaled.
4) To observe clinically its effects on the symptomatology and course of acute and chronic pulmonary diseases.

In the early investigations of penicillin mist and dust inhalations, the number of allergies and sensitivities was reported as 3 to 6 per cent.[1,2] However, following more extensive use of the method, local and generalized allergic reactions were found to be much higher (25 to 40 per cent). An even larger number of reactions was anticipated with streptomycin than with penicillin; for this reason the inhalation of streptomycin was discontinued until a less sensitizing form, dihydrostreptomycin sulfate, was introduced.

Procedure

The dihydrostreptomycin sulfate used in this experiment has been processed to a particle size of 44 microns or less, and packaged in 50 mg. amounts in the powder cup of a disposable plastic inhalor. Each powder cup is held in place by means of a plastic stylet and the inhalor is enclosed in an airtight glass tube (Figure 1). This inhalor is a simple plastic tube with a tapered rounded end (for oral or nasal use) and with an air hole at the opposite end. The cup containing the powder medicament slides freely up and down the cylindrical tube. The patient is instructed to take a sharp inhalation through the nose or mouth depending upon

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his need, being careful not to occlude the air hole at the bottom of the container. As the cup strikes the top of the inhalor, powder is released and is inhaled into the orotracheal or nasotracheal tract. At the close of the inspiratory phase the powder cup returns to the bottom of the chamber. Patients are instructed to remove the dispolator from nose or mouth on exhalation to avoid caking the powder particles with moisture. The use of this type of apparatus makes it possible for patients to receive treatment outside the hospital with a minimum of equipment and "gadgetry". No special care is required in the storage of these inhalors; they may be kept at room temperature without rapid loss of potency or absorption of moisture. The empty plastic dispolators are disposable.

Those to receive this therapy were selected from out-patients and from persons admitted to Wesley Memorial Hospital and Edwards Tuberculosis Sanitorium. Whenever possible, they did not receive any other medication during the course of the inhalations. Early in the investigation, the duration of treatment for each subject was determined bacteriologically as well as by the clinical progress made. Soon a routine was established whereby those with bronchiectasis and long standing bronchitis were given 10 days of treatment, while those with acute upper respiratory infections were given

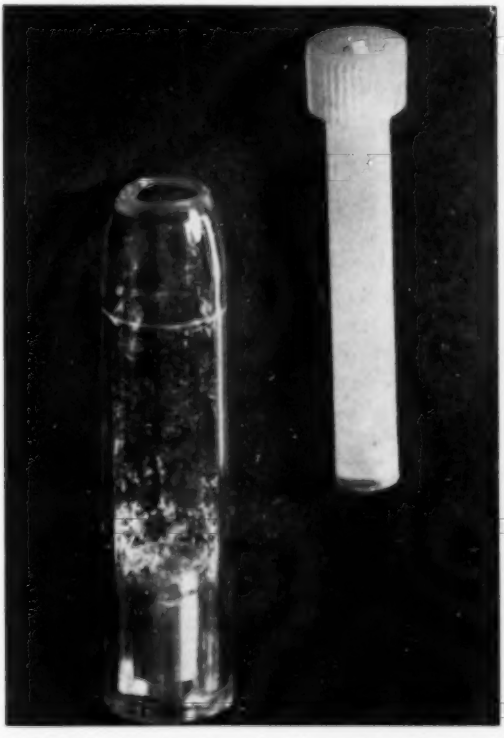

FIGURE 1: Dihydrostreptomycin disposable plastic inhalor.

three days. Inhalations for three days post operatively were considered adequate prophylaxis for the surgical case.

Patients received 100 mgs. of dihydrostreptomycin three times daily (six dispolators). Inhalations were continued until all the dust was inhaled, usually 16 to 30 inspirations. They were instructed to refrain from eating or drinking for one half hour following each treatment, to avoid washing down the dihydrostreptomycin dust from the posterior pharyngeal wall into the stomach.

Hourly blood samples were drawn from 16 patients following the inhalation of 100 to 500 mgs. of the dust, to determine the extent of systemic absorption through the capillary bed of the lungs.

Sputum specimens from all hospital patients were measured and cultured pre-inhalation and every third day of the treatment. After discharge from the hospital, further sputum specimens were collected and examined when they returned to the hospital for physical check-ups. The character of the cough was also recorded and the patients were observed for the relief of any other symptom or complaint. In the case of office patients, pre- and post-therapy cultures were made.

Results

Three hundred forty two persons with various affections of the upper and lower respiratory tract were treated with dihydrostreptomycin sulfate aerosol, of whom 125 had bronchiectasis. The remainder were treated for bronchitis, infections of the upper respiratory tract, sinusitis, the "common cold" syndrome of rhinitis and nasopharyngitis, pulmonary tuberculosis with tracheal lesions, and as a prophylaxis following and preliminary to certain surgical procedures. Seventy two were hospitalized and 270 were ambulatory.

Those with chronic conditions received 300 mgs. of dihydrostreptomycin sulfate per day (six dispolators) for 10 days. Patients with acute conditions and minor infections (upper respiratory infections, etc.) received three days of treatment depending on the particular condition involved.

Approximately 10 per cent (27) inhaled less than six cartridges (300 mgs.) The largest amount of the dust inhaled by one patient was 30 grams in an eight week period. Chart I tabulates the clinical diagnosis of the cases treated with dihydrostreptomycin dust.

This form of therapy is of greatest value for the bronchiectatic patient. In the preparation for pulmonary resection of those who have bronchiectasis, it is effective in providing a reduction of the volume of pulmonary secretions and a sterilization of the bronchial tree.

Cases of bronchiectasis not suitable for surgery can frequently be controlled by the use of dihydrostreptomycin dust aerosol, although it is obvious that there is no reversal of the underlying pathology. Early in the course of the experimental procedure it was planned to use both penicillin and dihydrostreptomycin for these cases. However, the infrequency of allergic reactions and favorable clinical response led to the use of dihydrostreptomycin sulfate dust alone. Especially for the office cases and the out-

CHART I: CLINICAL DIAGNOSIS

I. *Infections of the Upper Respiratory Tract:*	
A. Common Cold Syndrome (acute rhinitis and nasopharyngitis)	30
B. Acute and Chronic Sinusitis	3
C. Acute, Subacute and Chronic Laryngitis and laryngotracheobronchitis	25
II. *Infections of the Lower Respiratory Tract:*	
A. Chronic Bronchitis	60
B. Bronchiectasis	135
C. Tuberculous Bronchitis and Bronchiectasis	9
III. *Surgical Cases:* (Carcinoma of the Lung, Bronchiectasis, and those cases who have appreciable expectoration before and/or after surgery).	
A. Pre-operative Prophylaxis and Therapy	50
B. Post-operative Prophylaxis and Therapy	30
TOTAL	342

patients who come in for periodic visits, penicillin inhalations have been discarded and dihydrostreptomycin dust alone has been used.

Almost without exception, the bronchiectatic patient feels better following these treatments. His chest feels subjectively clearer; the sputum is less viscid and more readily expectorated, the amount is usually diminished and the odor is less offensive. Many can work without fatigue after a period of treatment with the dust.

It is obvious that the primary bronchial dilatation of bronchiectasis will not be affected by nebulization therapy and that these persons who have bronchial dilatation will still be subject to all the hazards of a deformed bronchial tree. If patients are to retain the benefits obtained from a course of nebulization it is probable that they will have to continue periodic courses of treatment indefinitely.

Children (even those who are refractory) are willing to take the inhalation treatments of dihydrostreptomycin and need no urging to continue the therapy.

Chronic bronchitis is another condition which improves markedly with aerosol therapy using dihydrostreptomycin dust. In cases of non-specific bronchitis, including bronchiectasis, it has proved the most satisfactory and effective available method of treatment; in a large majority of cases, it has reduced cough and expectoration markedly. In acute tuberculous bronchitis and tracheitis, where secondary infection is not a factor, the results have been disappointing; it is definitely less effective than intramuscular injections of streptomycin. The results in allergic bronchitis have not been spectacular; however, it has kept away secondary infections and often some improvement is seen in symptoms.

In asthmatic cases, the results have not been good; occasionally an improvement is noted when there is bacterial invasion.

Virus diseases, fungal diseases and respiratory diseases due to chemical agents are not affected by penicillin or dihydrostreptomycin aerosols, except in so far as secondary invaders are eliminated from the picture.

In acute bacterial infections such as nasopharyngitis, sinusitis, laryngitis, and acute tracheobronchitis, dihydrostreptomycin dust aerosol seems to reduce the length and severity of the disease.

Dihydrostreptomycin dust inhalations have been used in the pre-operative and post-operative management of persons with diseases of the chest and of other surgical patients in whom pulmonary infection exists or appears to be developing. This form of therapy appears, logically, to sterilize the bronchial tree.

Bacteriology

The bacterial data of the sputums studied confirms information gleaned earlier with the inhalation of wet streptomycin.[3] When penicillin alone was used, gram positive organisms disappeared from cultures and gram negative organisms grew profusely. When dihydrostreptomycin was added to the penicillin inhalations, in many instances the gram negative organisms disappeared and only yeast cells remained. When dihydrostreptomycin sulfate dust was used alone, gram positive organisms remained in the culture; however, it appeared from many of the cultures studied, that there was also a reduction in gram positives organisms. From the clinical results this is borne out, for dihydrostreptomycin dust inhalations alone appear to improve those conditions which appear to have their etiology from gram positive organisms alone, such as acute pharyngitis or acute naso-pharyngitis.

Blood Levels

Following inhalation, streptomycin is poorly absorbed from the lungs into the blood stream. Laurent et al., reported that it is retained in the lungs in an effective concentration for at least three hours; whereas penicillin is found in the blood stream in therapeutic amounts for two hours following an inhalation treatment.[4]

Blood samples were drawn at hourly intervals for four hours from 16 patients who had inhaled 100 to 500 mgs. of dihydrostreptomycin sulfate.

The Loo[5] method for determining the streptomycin level in the blood was used. In only one instance following the inhalation of 500 mgs. of the drug was slight inhibition of bacterial growth noted around the serum impregnated disk.

A drug deposited in the tracheobronchial tree cannot exert any local therapeutic action if rapid absorption prevents the building up of suitable concentration in the affected area, or if the drug is so finely broken up that it penetrates the deepest recesses of the lung, but is carried out again in the expired air.

Excessively rapid absorption is undesirable when an antibiotic concen-

tration is to be built up at a mucus surface. The normal physiological method of retaining moisture in the bronchial tree is by the provision of mucin, an unabsorbable, hydrophyllic colloid. This retardation of the drug may be of great value. Another means of retarding might be secured with the vasoconstrictor effect of adrenalin or ephedrine. From the blood level studies, it appears that dihydrostreptomycin dust exerts, mainly, a topical effect.

Spread of Dihydrostreptomycin Dust Particles in Pulmonary Tract

In order to determine the extent of the spread of the dust particles within the pulmonary tract, five patients were given a quantity of carbon particles to inhale. The washed carbon particles were dried in vacuo, screened through a 325 mesh seive to give particles of 44 microns or less, then sterilized by autoclaving at 15 pounds pressure for two hours and filled under aseptic conditions. After complete anesthetization of the pharynx and larynx (preparation for bronchoscopy), the patients inhaled the carbon in quantities similar to that in a dispolator of dihydrostreptomycin sulfate dust, and bronchoscopy was immediately performed to determine the progress of the particles. The carbon was visable in all the cases studied in this manner, throughout the tracheobronchial tree as far as the bronchoscope could visualize. Whether the bronchioles and alveoli were likewise laden with the carbon particles is still undetermined. The fact that the particles did line the main branches of the respiratory tract, was, however, definitely established.

Sensitivities and Allergic Manifestations

It is our general impression that dihydrostreptomycin dust is far superior to penicillin dust for inhalation purposes. There is less irritation during the inhalation of dihydrostreptomycin dust than there is with penicillin dust. No patient has refused to take the dust because of unpleasant taste and irritation, as has happened with penicillin dust. The occurrence of sore throat and velvety, thick, red tongue is much less frequent than with penicillin. In the entire group treated, there were six sensitivities or allergic reactions (1.7 per cent) and these were less intense and caused less discomfort to the patient and were of shorter duration than were the reactions following the use of penicillin inhalations. Five of these reactions were of a local type characterized by sore throat and tongue, one was a generalized maculopapular rash which disappeared promptly after the use of antihistamines and discontinuation of the drug. (This one had excellent results from the three days of dihydrostreptomycin therapy in spite of his generalized reaction.)

The allergic reactions occurred after three to four days of inhalation and disappeared fairly rapidly after discontinuation of the treatments. Often patients could continue the therapy if antihistamines were given along with the inhalations.

Clinically, the results with dihydrostreptomycin sulfate are superior to penicillin inhalations. Its main usefulness is in the bronchiectatic patient;

here clinical results have far surpassed those obtained with penicillin used in the same manner. Because dihydrostreptomycin dust caused less irritation than does penicillin, and fewer reactions with a satisfactory clinical response in a high percentage of cases, the members of the chest service have discontinued the combination of penicillin and dihydrostreptomycin inhalations and use dihydrostreptomycin inhalations alone.

SUMMARY

1) Three hundred forty two persons with infections of the upper and lower respiratory tracts were treated with dihydrostreptomycin sulfate dust inhalations.

2) The action of dihydrostreptomycin dust appears to be primarily topical.

3) One hundred twenty five bronchiectatic patients received one or more courses of 10 days treatment with dihydrostreptomycin dust aerosol with moderate to excellent improvement in their conditions.

4) The use of a small disposable unit makes this method valuable for the office patient, reducing the number of hospital patients and increasing the number of working hours.

5) The incidence of sensitivities and allergic manifestations is infrequent (less than 2 per cent) and of a mild nature.

6) Dihydrostreptomycin dust inhalations are superior to penicillin inhalations in the treatment of respiratory diseases.

RESUMEN

1) Se trataron 342 personas con infecciones de las vias respiratorias altas con dihidroestreptomicina (sulfato) con inhalaciones en polvo.

2) La acción de la dihidroestreptomicina en polvo parece ser primariamente tópica.

3) Se trataron 125 enfermos de bronquiectasia por medio de aerosol de polvo de dihidroestreptomicina con mejoría moderada o excelente de sus condiciones.

4) E luso de una unidad pequeña descartable hace este método valioso para el enfermo tratado en la oficina reduciendo el número de los enfermos que requieren hospitalización y las horas de trabajo.

5) La frecuencia de sensibilización y de manifestaciones alérgicas es baja (menos de 2 por ciento) y son moderadas.

6) Las inhalaciones de dihidroestreptomicina en polvo en inhalación es superior a las de penicilina en el tratamiento de las enfermedades respiratorias.

RESUME

1) Les auteurs ont traité 342 malades atteints d'affections des voies respiratoires, supérieures ou inférieures, par des inhalations de poudre de dihydrostreptomycine.

2) L'action de la poudre de dihydroestreptomycine est apparue d'emblée efficace.

3) 125 malades atteints de dilatations bronchiques furent traités par

une, ou plusieurs séries de 10 jours d'aérosols de dihydrostreptomycine. Ils en ressentirent un bienfait limité dans certains cas mais excellent dans d'autres.

4) L'utilisation de cette méthode est possible au bureau de consultation, elle réduit ainsi le nombre des malades hospitalisés et augmentent les heures de travail.

5) Les manifestations d'hypersensibilité ou d'allergie sont rares (moins de 2%) et de nature bénigne.

6) Les inhalations de poudre de dihydrostreptomycine sont supérieures à celles de pénicilline dans le traitement des maladies des voies respiratoires.

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Applications of Aspiration Lung Biopsy with A Review of the Literature*

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Introduction

Ninety-four aspiration lung biopsies were performed on 73 patients. These were divided into the four groups shown in Table I. Thirteen biopsies were done on normal lungs to show the histology and bacteriology (Group I); there were 29 biopsies of cases where the diagnosis was uncertain (Group II); the pathogenesis of the resolution of acute pneumococcal lobar pneumonia was investigated by means of 27 biopsies (Group III); and the pathogenesis of chronic lobar pneumonia by means of 20 biopsies (Group IV). In addition, hepatic cells were obtained in four biopsies and splenic cells in one. In all, seven cases were done after death but the term "biopsy" has been retained for the sake of convenience.

Tables II and III show the sex, race and age distribution of the 73 patients. Most of the biopsies were done at the New Somerset Hospital (Cape Town) which is exclusively for non-Europeans, and thus the majority of the patients were Colored or African.

The oldest living patient to be biopsied was Case 5, a colored woman of 74 years; the youngest was Case 68, a colored male infant of four months. The cases were numbered according to the order in which they were done.

Review of the Literature

In 1883 Leyden[1] performed the first aspiration lung biopsies on three cases of pneumonia and isolated organisms from one of these patients. Lung biopsy was subsequently, not infrequently used to obtain the causal organisms from patients with pneumonia.[2-15] When refined concentrated antiserum became available, lung biopsy played an important role in obtaining rapidly pure cultures of pneumococci especially in those cases without sputum.[16-21]

Colby[22] reported 12 cases of unresolved pneumonia "treated" by lung puncture with "good results".

Curphey[23] was the first investigator to examine lung biopsy material from lobar pneumonia histologically and he showed that the cellular reactions which were observed after the crisis in the resolving lung at autopsy also occurred during recovery.

In the field of diagnosis, lung biopsy has been used mainly for the diagnosis of pulmonary tumors.[24-40] Lipoid pneumonia has been diagnosed

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by lung biopsy.[41,42] Lung puncture has been used to confirm the diagnosis of pulmonary haemosiderosis.[43] Horder,[44] Lambert and van Ordstrand[39] and Godlowski[45] all visualized a much wider field of application. Horder considered that the procedure was indicated in any cases of consolidation where sputum cultures failed to show the causal organisms, and in cases of lung abscess and bronchiectasis. Lambert and van Ordstrand diagnosed several cases of bronchogenic carcinoma that had been diagnosed clinically as benign inflammatory conditions, and in two cases "lung tumors" were proved to be unresolved pneumonia and fuso-spirochaetal lung abscess. Godlowski performed 75 biopsies on normal men and women and described the cells that were present in the normal "pulmogram". He showed that the lung of the heavy tobacco smoker contained many more macrophages than that of the non-smoker. He suggested that lung biopsy might be used in various pathological conditions such as pneumoconiotic and acute and chronic inflammatory processes.

Lavalle[46] stated that, in tuberculosis, puncture of the "nucleus" in the lung would release autovaccines and haptens into the blood stream and he reported favorable results in 100 cases.

TABLE I

Group	Type of Case	No. of Patients	Total No. of Biopsies	No. of Biopsies Done After Death
Group I	Normal lungs	13	13	3
Group II	Diagnostic cases	24	29	3
Group III	Acute pneumonia with normal resolution	21	27	0
Group IV	Chronic lobar pneumonia	13	20	0

TABLE II: SEX AND RACE DISTRIBUTION OF THE SEVENTY THREE PATIENTS

Race	Sex	No. of Patients
Colored	Male	37
Colored	Female	14
African	Male	11
African	Female	7
Moslem	Male	2
Moslem	Female	0
Indian	Male	1
Indian	Female	0
European	Male	1
European	Female	0

Technique

The technique employed was simple and yielded material for both histology and bacteriology.

No premedication was used. The situation of the biopsy depended on the site of the affected area and no lobe of the lung was exempt. After the death of Case 34 all patients were placed in the horizontal position on the purely theoretical assumption that if air embolism did occur then the air was less likely to pass to the brain.[38]

About 4 ml. of 2 per cent planocaine were used to infiltrate the skin, underlying muscle, pleura and the superficial lung tissue. A small stab incision was made in the skin using a No. 11 Bard-Parker blade; this facilitated the introduction of the needle and prevented contamination by skin cells.

The biopsy needle (18 gauge, 9 cm. in length with a short bevel and a well fitting stylette) was then introduced through the skin incision and into the lung. The stylette was then removed and a 20 cc. B-D Lok-Syringe attached. The plunger was withdrawn to the 20 cc. mark. With suction maintained the needle was then inserted 2 to 4 cm. further into the lung and then withdrawn to its original position; sufficient material could be obtained from one insertion. The negative pressure was then released and the needle with syringe attached withdrawn. In the one infant in the series sufficient material was obtained by the use of an intramuscular needle and a 5 cc. syringe.

After the syringe and needle had been withdrawn, a drop of the material was expelled onto a non-sterile glass slide, care being taken not to touch the slide with the needle tip. If sufficient fluid was still present in the needle, a drop was placed onto a blood agar plate, a drop onto a slope of Lowenstein medium, and the rest into a small capped bottle of serum broth. If only a small amount of fluid remained in the needle then a few drops of serum broth were aspirated into the needle and syringe and this material used for the inoculation of the media. The drop on the blood agar plate

TABLE III: AGE DISTRIBUTION OF THE SEVENTY THREE PATIENTS

0- 9 years	2
10-19 years	9
20-29 years	23
30-39 years	12
40-49 years	16
50-59 years	8
60-69 years	1
70-79 years	1
80-89 years	1

was "plated out" in the usual way. The original drop of bloody fluid on the slide was distributed over as many slides as possible and crushed smears made by placing a clean slide crosswise over the material on the other slide and crushing and smearing at the same time.

A little collodion soaked cotton wool was applied to the small skin incision, and the patient allowed to return to the sitting position.

A simple "non-touch" technique was used and in none of the cases was there any sign of infection of the puncture site. Direct roentgenological guidance was not used. An x-ray film of the chest was done on the following day or as soon as possible thereafter to check for the presence of pneumothorax.

At the same time as the biopsy, sputum (if available) was plated out onto blood agar and incubated at the same time as the biopsy cultures.

The slide preparations were allowed to dry at room temperature and were then stained; one with haematoxylin and eosin[30,34] one with Leishman stain,[45] one by Gram's method, and the last one by Ziehl Neelsen's method. In the last few biopsies an additional slide was stained by a method by which in the same slide the cells, fibrin and pneumococci could all be clearly demonstrated.[47,48]

It was not necessary to have the patient hold his breath during the biopsy.

Complications of Lung Biopsy

Eighty-three biopsies on living patients are analyzed. The four cases where liver cells were obtained and the seven where "biopsy" was done after death are not included.

No case of empyema occurred. There was no evidence that the cases of tuberculosis were any worse after the biopsy. In the one case of carcinoma the patient deteriorated at the same rate after as before biopsy.

Haemoptysis occurred in 34.9 per cent of cases. Of these moderate haemoptysis (more than a tablespoonful of bloody sputum) accounted for 8.4 per cent and small haemoptysis (slight blood streaking of the sputum) for 26.5 per cent. The largest haemoptysis was five tablespoonfuls of heavily blood stained sputum.

Slight pain was a complaint in 10 cases (12 per cent) and of these seven had small pneumothorax. Pneumothorax occurred in eight cases (9.6 per cent) and in four of these the technique was probably at fault. The pneumothoraces were usually small and shallow. In one (not included in the series as no biopsy was performed), a 78 year old man with considerable emphysema, tension pneumothorax occurred after the infiltration of the local anaesthetic.

In two patients there was cough, dyspnoea and haemoptysis for a few minutes after the biopsy. One experienced transient syncope about a minute after the biopsy. One about a minute after biopsy had small haemoptysis, sweated and said that he felt a "shock" in the left corner of his mouth and in his left hand; he then vomited and felt normal again. This may possibly have been due to a small air embolus.

There was one death in the series, Case 34 a colored male of 45 years

with widespread bilateral pulmonary tuberculosis, tuberculous meningitis and asbestosis. The biopsy was done with his head raised on one pillow as he complained of considerable dyspnoea when lying absolutely flat. About 10 seconds after biopsy he became unconscious, pale, rigid, and pulseless. Adrenalin was given and oxygen commenced. During the next 30 minutes he rapidly improved and in the next 15 hours he appeared to be recovering. However, during the night there were twitchings of the left side of his face and his left arm, his pulse became rapid and weak and respirations Cheyne-Stokes in type and he died 17 hours after the biopsy had been performed. At autopsy no air emboli were found in the cerebral vessels, but it seemed likely that the needle had entered a cavity with large vessels running on its inner surface. There seemed little doubt that this death was related to the biopsy and an air embolus to the brain was possibly the etiological factor.

In all, 45.8 per cent of cases showed complications, of which the vast majority were of a minor character.

In many cases two biopsies were done on the same patient and two cases were subjected to three biopsies each. One case had two done on the same side within 15 minutes of each other without any complication.

A feature of lung biopsy is that if complications are going to occur they do so within five minutes of removal of the needle from the chest.

The incidence of complications as a whole differed but little between the normal, diagnostic and pneumonia cases. The distribution of complications was fairly equal in the various age groups and there was an equal incidence in the male and female patients. When the situation of the biopsy was in the upper lobes the total incidence of complications was 70 per cent and 66.7 per cent for the right and left respectively (but few biopsies were done on the left upper lobe) and the corresponding figures for the right and left lower lobes were 36.5 per cent and 33.3 per cent respectively. There seemed no obvious reason for this apparently greater risk of sequelae after biopsy of the upper lobes of the lung.

In four biopsies done on the right side liver cells were obtained. In all these cases the needle was inserted into the area where physical signs were maximal.

In one "biopsy" done after death at the left base in the anterior axillary line cells from the spleen were aspirated.

Lung Biopsy of the Normal Lung

The Sterility of the Normal Human Lung:

There is no direct information available as to whether the human lung is normally sterile. In the present series there were 13 normal cases. The first 10 were living persons whose lungs were both clinically and radiologically normal. The final three normal "biopsies" were done soon after death, namely five hours, one hour and five minutes respectively. In these cases smears stained by Gram's method showed in the first two cases organisms but there were none from the biopsy done almost immediately after death. One may assume that these organisms were postmortem in-

vaders. Cultures from the biopsies of the 10 living cases showed no growth in six and the remaining four showed scanty growth of organisms that were obviously contaminants.

It seems probable that the normal human lung is sterile.

The Normal Pulmogram:

The term "pulmogram" means the cellular analysis of a smear of the material obtained by aspiration lung biopsy.[45] Cells may be present which have their origin from the skin and thoracic wall, the pleura, the lung itself and from the blood in the pulmonary vascular tree.

In none of the smears were there cells which might have come from the skin or thoracic wall.

Cells derived from the pleura were found in only occasional cases. Red and white cells from the pulmonary vessels were present in all pulmograms. Cells derived from the lung tissue itself were ciliated bronchial epithelial cells, ciliated bronchiolar epithelial cells, non-ciliated bronchiolar epithelial cells, alveolar epithelial cells, three types of macrophages (small macrophages, dust cells, and alveolar histiocytes), and non-nucleated plates. Masses of crushed tissue were of two types, namely a rather openwork type consisting of lung "parenchyma," and a dense connective tissue which probably had its origin from the peribronchial or peribronchiolar regions. Large and small black particles were often found lying free (not within cells) in the "parenchyma" and connective tissue. These were probably inhaled dust and other foreign material.

Lung Biopsy Used for Diagnostic Purposes

Twenty-nine lung biopsies were performed on 24 persons; three of these "biopsies" were done after death. The varied conditions investigated are shown in Table IV. For the sake of brevity only a few case reports will be given and these will be considerably simplified.

TABLE IV: THE TYPES OF CASES ON WHICH LUNG BIOPSY WAS PERFORMED FOR DIAGNOSTIC PURPOSES

Type of Case	No. of Cases
Pulmonary tuberculosis	8
Various pneumonias	7
Pulmonary infarction	2
?Rheumatic pneumonia	2
?Uraemic lung	1
Peripheral carcinoma of the lung	1
?Amoebic abscess of the lung	1
Bronchiectasis and lung abscess	1
Congenital cystic lung	1
TOTAL	24

Pulmonary Tuberculosis:

In the eight cases of pulmonary tuberculosis, five showed tubercle bacilli either on direct smear or culture or both; in one tuberculous empyema was suspected; and in two it could be stated that the process was a chronic inflammatory one.

Case 5: Colored female, 74 years of age, presented with haemoptysis and x-ray film showed a diffuse shadow involving the right upper lobe. The diagnosis was either carcinoma or tuberculosis and sputa were negative for tubercle bacilli. The first biopsy showed a low grade inflammatory lesion and the material was sterile; but tubercle bacilli were cultured from the second biopsy. The diagnosis was confirmed by autopsy about a month later.

Case 68: A colored male infant of four months had had a cough for two weeks. His temperature varied from 99 to 102 degrees F. and x-ray film showed a homogeneous consolidation of the whole of the right upper lobe. The x-ray film appearance remained unchanged in spite of long continued treatment with penicillin, sulphadiazine and then terramycin. Caseous material was obtained by lung biopsy and tubercle bacilli were present on the direct smear and were cultured.

Unusual Pneumonias

In this group lung biopsy was used to diagnose two cases of bacterial pneumonia after death where the antemortem diagnosis had been pulmonary infarction and tuberculosis; one case was shown to be pneumonia, probably pneumococcal, associated with acute nephritis; a chronic staphylococcal pneumonia was diagnosed mainly from the biopsy findings; a chronic bronchopneumonia was shown to be pathologically similar to chronic lobar pneumonia; pulmonary eosinophilia was excluded in a case of allergic asthma with bronchopneumonia; and in one case biopsy did not help to elucidate the etiology of the pneumonia.

Case 59: A colored male of 58 years gave a history suggestive of an acute pneumonia two months before admission and he was admitted because of dyspnoea. There was collapse of the right lower lobe for which no cause could be found. He remained slightly pyrexial in spite of long courses of antibiotics. Lung biopsy showed large masses of fibrin with scanty polymorphs and macrophages and groups of pleomorphic cells which were probably metaplastic alveolar cells; from cultures there grew a pure growth of staphylococcus aureus sensitive to penicillin and streptomycin. He was again given antibiotics and lung aspiration a month later showed in addition cells resembling fibroblasts and again staphylococcus aureus, now insensitive to penicillin, was grown in pure culture. This suggested a chronic staphylococcal pneumonia which had gone on to fibrosis.

Pulmonary Infarction, Rheumatic Pneumonia and Uraemic Lung:

These cases all showed similar histological pictures in the biopsy smears. There was fibrinous or albuminous material with rather scanty cells mainly small macrophages. The cultures were sterile.

Carcinoma of the Lung, Amoebic Abscess, Lung Abscess and Congenital Cystic Lung:

The case of carcinoma showed a well marked, rounded, peripheral opacity in the right upper lobe and the biopsy material contained groups of malig-

nant cells. Amoebic pus was aspirated when biopsy was done on a patient with a mass postero-laterally in the right costo-phrenic angle. Lung biopsy of a case with an apparent lobar pneumonia both clinically and radiologically revealed the presence of pus in the lung. Resolution was somewhat delayed and a subsequent bronchogram showed gross bronchiectasis of the affected lobe. A patient with an x-ray film suggestive of congenital cysts of the right upper lobe produced only one specimen of sputum and from this Friedlander's bacillus was cultured. Lung biopsy showed a sterile mild inflammatory condition and the diagnosis of congenital cystic lung or cystic bronchiectasis was confirmed by bronchogram.

It should be emphasized that the lung biopsy material must be considered together with a clear picture of the clinical state of the patient. It was not often that the lung biopsy material alone would give the diagnosis. The chief value of biopsy was when the findings were compatible with one diagnosis and made other diagnoses unlikely. It must be realized that the diagnostic interpretations of the above cases were based on an experience of only 94 aspiration biopsies and that there was little or no literature with which one could compare results.

In the lung biopsy material of four cases the presence of classical asbestos bodies was an incidental finding. Three of these cases had acute pneumococcal pneumonia and one had widespread pulmonary tuberculosis. In none of the cases was there history of contact with asbestos.

The Pathogenesis of the Resolution of Acute and Chronic Lobar Pneumonia

The pathogenesis of lobar pneumonia, which runs its course uninterrupted by specific therapy, is well known; it is uncertain what changes occur in the lung when the pneumococci are destroyed with the assistance of sulphonamides or penicillin. To investigate this problem lung biopsies were done on living patients at various stages of their disease before and after therapy.

It is necessary to define the terms acute and chronic lobar pneumonia. Acute lobar pneumonia is one which runs an uncomplicated course to complete clinical and radiological resolution within 30 days (an arbitrary figure) of the commencement of chemotherapy or antibiotic therapy or both. Chronic lobar pneumonia is one which presents in a similar manner to acute pneumonia and appears at first to respond like the acute case except that the temperature is frequently more persistent; although the patient's general condition is good, clinical and radiological signs of consolidation remain for more than a month, but eventually complete resolution does occur without any serious residue. It is important that after the acute stage is over, these patients look and feel well and are usually apyrexial. The only abnormalities are the physical or radiological signs of consolidation. This condition should really be called: "lobar pneumonia with slow or delayed resolution."

The therapeutic regime for all cases of pneumonia was penicillin 200,000 units intramuscularly and sulphatriad two grammes (four tablets) orally

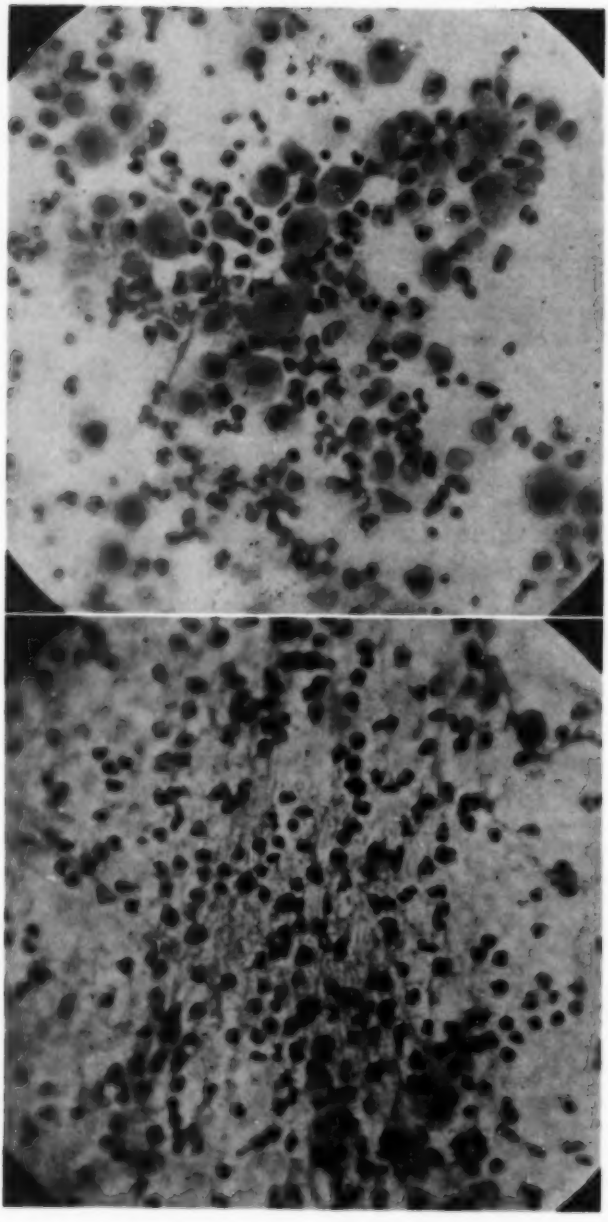

FIGURE 1 FIGURE 2

Figure 1: Red Hepatisation. High Power.
Figure 2: Early Resolution. High Power.

on admission; then 100,000 units penicillin and one gramme (two tablets) of sulphatriad four hourly. For convenience, the term "chemotherapy" is used to embrace both sulphonamide and penicillin therapy.

Twenty-seven lung biopsies were performed on 21 cases of acute pneumococcal lobar pneumonia. Twenty biopsies were done on 13 with chronic lobar pneumonia. Although this was a small series of cases the results showed a significant pattern. The number of biopsies of each stage of the pneumonia is shown in Table V.

TABLE V: TO SHOW THE NUMBER OF LUNG BIOPSIES PERFORMED AT THE DIFFERENT STAGES BEFORE AND AFTER ONSET OF CHEMOTHERAPY

Time from Onset of Chemotherapy Days	Acute Pneumonia No. of Biopsies	Chronic Pneumonia No. of Biopsies
0	8	2
0-1	5	1
1	2	0
2	2	1
3	2	1
4	2	1
5	3	1
6	2	3
11	0	2
18	0	1
24	0	1
26	0	1
29	0	1
33	0	1
42	0	1
44	0	1
Uncertain	1	0
Insufficient material	0	1

Bacteriological Findings:

In all cases which had received no treatment pneumococci were seen on the smear stained by Gram's method and cultured from the biopsy material. In two patients pneumococci were cultured from the biopsy material but not from the sputum plated out at the same time. Pneumococci were neither seen nor cultured from biopsy material when the patient had been on chemotherapy (either sulphonamides or penicillin) for more than 24 hours. Even in cases of chronic lobar pneumonia which were still pyrexial and where signs of consolidation were marked, the lung biopsy material was

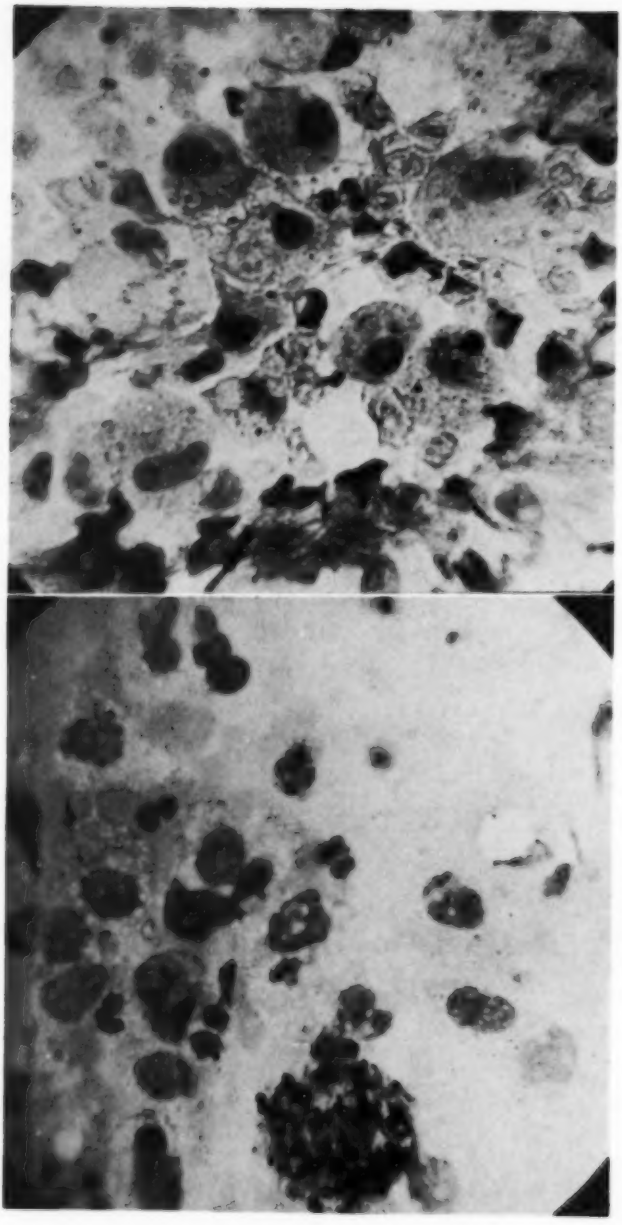

FIGURE 3 FIGURE 4

Figure 3: Fairly Well Advanced Resolution. Oil Immersion.
Figure 4: Advanced Resolution. Oil Immersion.

sterile. In those chronic cases where a significant organism was grown from the sputum—beta-haemolytic streptococci in Cases 29 and 53, and coagulase positive staphylococcus aureus in Case 65—the biopsy material was sterile. Thus cases of chronic pneumonia, on the evidence of organisms cultured from the sputum, may wrongly be attributed to a resistant persisting infection.

Histological Findings:

Before treatment the histological picture of the lung, in both acute and chronic cases, was that of red hepatisation. There were large masses of fibrin and numerous well preserved polymorphs (Figure 1). During the first day of treatment there was no change in the pathological picture. After two days of adequate chemotherapy, the histology was that of early resolution—large masses of fibrin were present with polymorphs (often degenerate) and small macrophages in almost equal numbers; the macrophages frequently showed ingested polymorphs (Figure 2). After three or more days of therapy, resolution was established. In fairly well advanced resolution fibrin was present associated with numerous small macrophages and infrequent polymorphs which were occasionally seen within macrophages (Figure 3). In advanced resolution the fibrin was less in amount and was becoming granular, small macrophages were numerous and polymorphs were scanty (Figure 4).

Where resolution was normal it was probable that the macrophages rapidly removed the fibrin and finally left the lung which then returned to normal. The macrophages were possibly destroyed finally in the cells of the reticulo-endothelial system. Biopsies of cases with normal resolution were not done later than six days after the commencement of chemotherapy. It would appear that with chemotherapy the stage of gray hepatisation has ceased to exist.

The chronic pneumonia cases showed the same changes in the first six days after the beginning of therapy but one case showed an apparently rather poor initial polymorph response and in another the macrophage response was somewhat delayed. In those cases done after six days there appeared, in addition to the small macrophages, a fair number of larger cells which differed from the classical "dust cell"; these "chronic pneumonia macrophages" were about twice the size of the small macrophages but were otherwise similar; there was a single nucleus, vacuolated cytoplasm and scanty or absent ingested particles. These were probably simply older forms of the small macrophages. These large macrophages were present in small numbers during normal resolution but, as the duration of resolution became prolonged, they were seen more frequently. All the cases biopsied more than 18 days after the onset of chemotherapy showed a similar histological picture; macrophages and fibrin were present irrespective of the duration of the pneumonia.

Cells showing the intermediate stages between lymphocyte and monocyte and monocyte and small macrophage were noted and these cells were termed "intermediate cells". They were infrequently seen during red hepa-

tisation but became fairly numerous during early and fairly well advanced resolution and were still common in advanced resolution. This intermediate cell response, which seemed to just precede the macrophage response, lent support to the theory[49,50] that the macrophages were derived from the mononuclear cells of the blood. In the cases with slow resolution the number of intermediate cells varied considerably from fairly numerous to infrequent and there appeared to be no correlation between the number of intermediate cells and the duration of the pneumonia.

It would appear that in chronic lobar pneumonia the fibrin is not so readily removed, as in the cases with normal resolution, and the macrophages become older and new ones enter the lung; the number of intermediate cells do not indicate that "reinforcements" are called for urgently. The process remains an indolent one of macrophages and fibrin with resolution continuing slowly until final clearing of the fibrin results. It would appear that the macrophages were at fault either quantitively or qualitatively; either insufficient macrophages were mobilized and fewer macrophages took longer to remove the fibrin, or sufficient macrophages arrived in the lung but were not as efficient in removing the fibrin as normal macrophages and thus the process took longer. The answer was not given by the present investigation. Whatever the basic cause, the fault is probably in the "soil" not in the "seed". Case 19 was admitted to the hospital in 1949 with pneumonia of the right upper and middle lobes and this ran a chronic course; a year later he was admitted with pneumonia of the left lower lobe and again there was considerable delay in resolution. This would suggest an intrinsically poor reaction capability in respect to pneumonia but the patient had a rheumatic heart which might have been a factor affecting both lungs. However, there was no cardiac enlargement and no symptom, sign or history of heart failure, and the murmurs were heard with difficulty. The cause of delayed resolution has been attributed, in the past, to the presence of coexisting disease but in the present series of both acute and chronic cases factors such as anaemia, alcoholism, smoking, attacks of bronchitis, previous attacks of pneumonia and syphilis were frequent. Case 41 had numerous asbestos bodies in his lung and a positive Wassermann reaction but resolution was complete in 23 days; Case 30 had coexisting severe acute nephritis but resolution was normal. The bias of the writer is in favor of the theory that some people will respond to the treatment of primary pneumococcal lobar pneumonia by rapid resolution and others by slow resolution irrespective of the presence of concomitant pathological conditions.

Clinical Aspects:

In the cases of acute pneumonia it was of great interest to try and relate the general condition of the patient and the physical signs in the chest to the underlying pathological process. It was found that the physical signs gave little indication of the pathological state of the underlying lung. All cases showed some diminished movement of the affected side and most cases were relatively dull to percussion irrespective of whether the lesion

was active or resolving. Similar comments may be made in respect to alterations in vocal fremitus and vocal resonance. Breath sounds were often bronchial in spite of the presence of the cellular changes of advanced resolution; crepitations were found associated with both red hepatisation and advanced resolution and were sometimes absent in cases of both these types of pathology. In the individual case one occasionally found diminished dullness or the appearance of or increase in the number of crepitations as the lesion resolved. Probably the most valuable guide, in determining progress during the first few days after the onset of chemotherapy, was the general condition of the patient. If he became non-toxic and apyrexial and expressed a feeling of well-being then one could usually correctly predict that resolution was progressing satisfactorily.

An attempt was made to fit the 13 cases of chronic pneumonia into a definite clinical group without taking into consideration the duration of the illness. All these cases were of the 30 to 55 year age group, there was little significance in the sex distribution or in the lobe of the lung affected, and in most cases the mode of onset was similar to that of the acute case. The leucocyte count was usually high with a high percentage of neutrophils. The response to chemotherapy was striking and rapid but although the temperature fell by crisis in nine of the 13 cases there continued a slight intermittent or remittent pyrexia for from eight to 30 days. A small associated sterile pleural effusion was more frequent in the chronic than the acute cases. Residua visualized on x-ray films, such as thickened pleura or obliterated costo-phrenic angle, were found occasionally in both acute and chronic cases. Bronchograms in two of the chronic cases showed no bronchiectasis and in one case there was a mild dilatation of the branch to the posterior basal segment. It was unlikely that the cases of chronic lobar pneumonia (where no positive cultures were obtained) were due to a virus as there was the acute illness, the severe symptoms and signs, the lobar distribution of the lesions, the high leucocyte counts, and the immediate general response to chemotherapy.

It was extremely difficult to predict whether pneumonia would undergo normal resolution or become chronic. However if the patient responded generally to chemotherapy but continued to have a slight intermittent or remittent pyrexia for more than five or six days and developed a small pleural effusion then he might go on to the "chronic stage". The local physical signs on admission gave no indication of prognosis from this point of view.

SUMMARY

1) The literature on aspiration lung biopsy is briefly reviewed.

2) In the present series 94 biopsies were performed on 73 persons.

3) The technique is described and the possible complications and dangers discussed.

4) Thirteen biopsies were performed on patients with normal lungs. Cultures were sterile. The various cells seen in the normal pulmogram are mentioned.

5) Twenty-nine biopsies were done on 24 patients for diagnostic purposes. These included cases of tuberculosis, unusual pneumonias, pulmonary infarction, rheumatic and uraemic lungs, peripheral carcinoma, amoebic abscess, bronchiectasis and lung abscess, and congenital cystic lung. In four cases asbestos bodies were present in the biopsy material as an incidental finding.

6) Twenty-seven lung biopsies were performed on 21 cases of acute lobar pneumonia, and 20 biopsies were done on 13 patients with chronic lobar pneumonia. The bacteriological and histological changes that were present before and after chemotherapy are described. The findings in the cases with delayed resolution are given and discussed. In the cases of acute pneumonia an attempt was made to relate the general condition of the patient and the physical signs in the chest to the underlying pathological process. The possibility of fitting the cases of chronic lobar pneumonia into a definite clinical group is discussed.

7) Aspiration lung biopsy is a useful diagnostic and research procedure.

Acknowledgements: I am greatly indebted to Professor F. Forman and Dr. A. Landau for their interest, encouragement and helpful criticism. The expenses of this investigation were defrayed by a grant from the University of Cape Town Staff Association Fund.

RESUMEN

1) Se ha revisado la literatura sobre la biopsia por punción pulmonar.

2) En la serie que se estudia, se hicieron 94 biopsias en 73 personas.

3) Se describen la técnica y las posibles complicaciones y peligros.

4) Se hicieron 13 biopsias en personas con pulmones normales. Los cultivos fueron estériles. Las diversas celdillas encontradas en el pulmonograma normal, se mencionan.

5) Se hicieron 29 biopsias en 24 enfermos con fines diagnósticos. Estos casos incluyeron tuberculosos, neumonias inusitadas, infarto pulmonar, pulmones reumáticos y urémicos carcinoma periférico, absceso amibiano, bronquiectasia y absceso pulmonar y pulmón quístico congénito. En cuatro casos se encontraron cuerpos de asbestos como hallazgo incidental.

6) Se hicieron 24 biopsias pulmonares de 21 casos de neumonía lobar aguda y 20 biopsias se hicieron en enfermos con neumonía lobar crónica. Los cambios bacteriológicos e histológicos que existían antes y después de la quimioterapia, se describen. Los hallazgos en los casos con resolución retardada se presentan y discuten. En los casos de neumonía aguda, se hace un intento para relacionar el estado general del enfermo y los signos físicos en el tórax con la antomía patológica subyacente. Se discute la posibilidad de acomodar los casos de neumonía lobar crónica dentro de un grupo definido.

7) La biopsia por aspiración pulmonar, es un procedimiento útil de diagnóstico y de investigación.

RESUME

1) Revue rapide de la littérature médicale concernant les examens anatomo-pathologiques du poumon par aspiration.

2) L'auteur rapporte 94 examens concernant 73 individus.

3) Il décrit la technique et met en discussion ses complications et ses dangers.

4) Après 13 examens pratiqués sur poumons normaux, les auteurs exposent les différents aspects des cellules prélevées sur le poumon normal.

5) 29 examens furent pratiqués sur 24 malades dans un but de diagnostic. Il s'agissait de tuberculose, de pneumopathies atypiques, d'infarctus pulmonaires, de poumons de rhumatisants, d'abcès amibiens, de bronchectiectasies, d'abcès du poumon, de poumon kystique congénital. Dans 4 cas l'aspiration mit incidemment en évidence des corps asbestosiques.

6) 27 examens eurent lieu à l'occasion de 21 cas de pneumopathie lobaire aiguë et 20 sur des malades atteints de pneumopathie lobaire chronique. L'auteur décrit les constatations bactériologiques et histologiques avant et après chimiothérapie. Les constations qui furent faites lors d'évolution lentement résolutive sont exposées et discutées. L'auteur essaye de mettre en évidence la relation qui, dans les cas de pneumopathies aiguës, unit les signes généraux et les signes physiques aux processus anatomo-pathologiques. Il se demande s'il est possible d'assigner une place nosologique définie aux cas de pneumopathie lobaire chronique.

7) L'examen anatomo-pathologique des produits obtenus par aspiration pulmonaire est un procédé de recherche et de diagnostic de grande utilité.

References will appear in reprints.

The Role of Perforation of Hilar Lymph Nodes Into the Bronchial Tree of Adults

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In recent years it has been apparent that there is a decreasing incidence in the frequency of the classical caseous, ulcerative type of bronchial tuberculosis. However, localized processes appearing in the bronchial wall are observed much more often, probably as the result of involvement of the hilar lymph nodes. Increasing significance has been attached to these phenomena, particularly in adults, where attention has been drawn to the possible relation of perforation of a node into the bronchial tree and the pulmonary extension of the tuberculous disease. This aspect of primary tuberculosis in children is generally recognized. It has a well defined symptomatology in which a lymph node perforation into the bronchial tree is recognized as the most serious form, often indicating the beginning of tertiary pulmonary tuberculosis. This opinion has been strengthened within the last few years by a vast number of bronchoscopic examinations especially by the French school (Mounier-Kuhn, Le Jeune, Dufourt, Lemoine, etc.). Although reports on identical developments in adults have recently increased in number, with many cases of perforation of the bronchial walls being particularly stressed (Gyselen et al., Levi-Valenti, Boucher), clinicians and pathologists have generally refused to acknowledge such post-primary forms in adults, maintaining that there are different anatomic conditions in the bronchi and a relatively rare appearance of primary tuberculosis in adults. However, late primary infection today is a common fact as Schwartz and Uehlinger indicated in various papers based on pathological-anatomical examinations which demonstrated that bronchogenic dissemination by perforating hilar lymph nodes is quite common. Furthermore, in thoracic surgery in cases of tuberculosis one almost always finds a large, partly caseous mass of lymph nodes closely linked to the bronchus from which it can be detached only with great difficulty.

We would like to give a detailed account of our experiences in this important matter.

In the 1228 adult tuberculous patients bronchoscoped within the last two years (with a total of 1567 bronchoscopies) we found 38 acute perforations into the larger bronchi (Figure 1A). As all our cases are sanatorium patients who when they first fell ill were cared for elsewhere for weeks or even months, we are dependent on residual findings in late cases, the correct interpretation of which is often difficult (Figure 1B). In considering 81 such cases as residues of hilar perforation the diagnosis was established when the findings were either endoscopically clear or the patient showed typical findings in the lungs, particularly bronchogenic dissemination. It is possible that these figures are too low; first, because

not all perforations lead to lung complications, or the changes may already have disappeared. Secondly, residues in the bronchial walls usually produce no symptoms. Thus, perforations and residues actually show up in approximately 10 per cent of the bronchoscoped patients. The age of the patients with ascertained perforations varies largely. In almost 70 per cent the age was 18 to 30 years; two cases were in the 50's and one was in his 60's. Of the 38 cases there were only seven men. Symptoms are not reliable; only twice did patients expel suspicious material, and once it was necessary to remove a calcareous body in connection with a perforation into the bronchus of the mediobasal segment of the right lower lobe. Irritative cough appears more often, while stridor is more dependent on the degree of granulation than on the perforation itself. Often the sputum was suddenly positive, but it was generally some change in the lungs that led to the suspicion of a lymph node perforation into the bronchial tree.

The following case may serve as an example:

1) Two years after primary tuberculosis this 18 year old girl, a factory worker, developed extensive and cavernous tuberculosis of the right upper lobe. Bronchoscopy showed a broad new perforation in the medial wall of the right main bronchus. Conservative treatment with streptomycin, PAS and INH led to complete recovery (Figures 2 and 3).

We are certain that in this case bronchogenic dissemination caused tuberculosis of the lungs, a development regarded up to now as quite unusual. But recalling the fact that a great part of non-tuberculous lung disease originates in functional disturbances in the bronchus, particularly when drainage and the amount of secretion are unbalanced, it appears likely even from a clinical point of view that tuberculous hilar nodes can play a decisive part in the development of tuberculosis of the lungs. Actually, this may occur in a manner similar to the progress of tuberculous

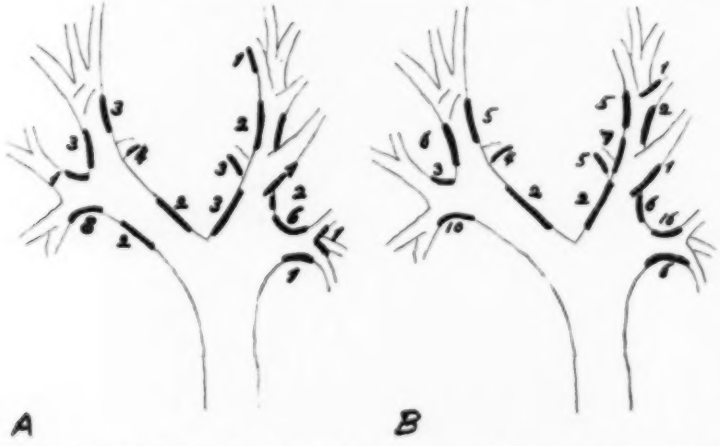

FIGURE 1: (A) Site of 38 perforations of tuberculous nodes into the bronchial tree. (B) Site of residual findings in 81 cases interpreted as due to previous perforation of tuberculous nodes into the bronchial tree.

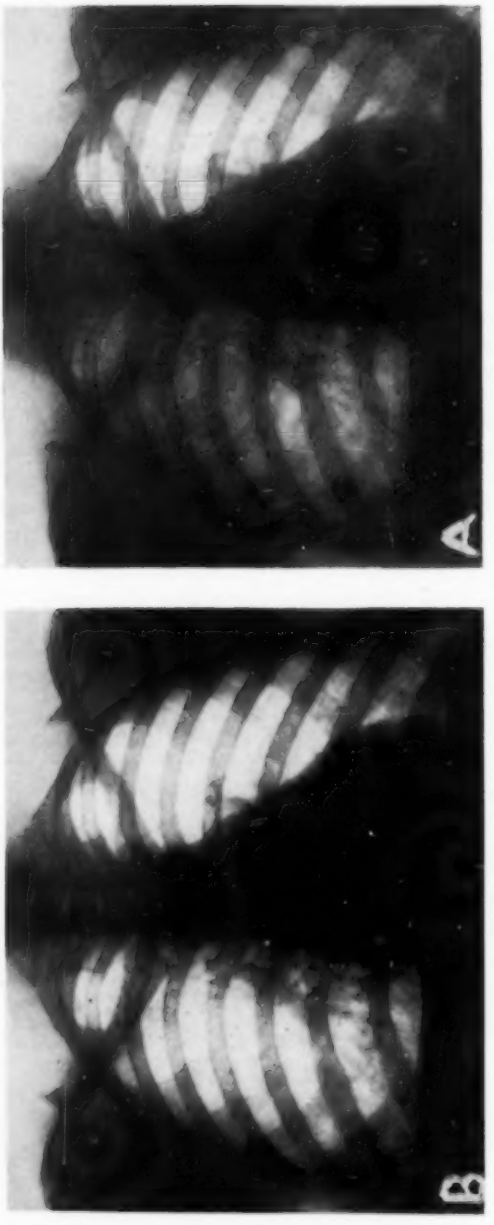

FIGURE 2. CASE 1: (A) Tuberculosis of right upper lobe. Bronchoscopy revealed perforation of medial wall of right main bronchus.—(B) Film one year later.

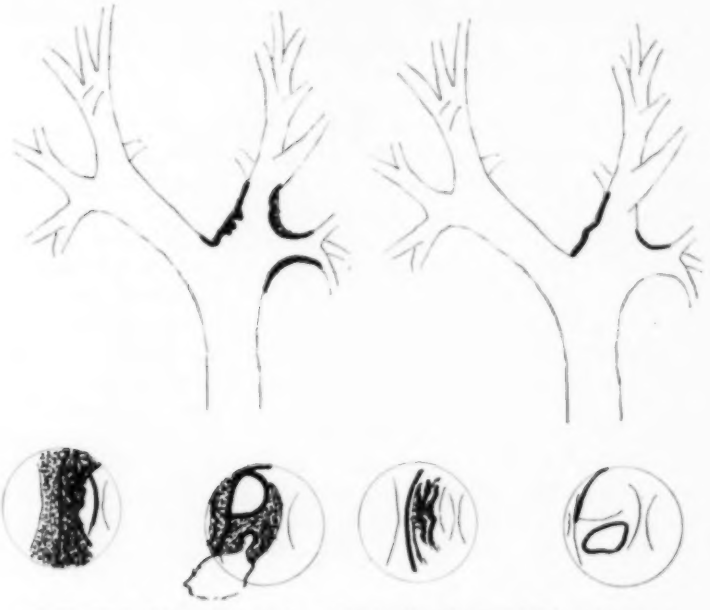

FIGURE 3, CASE 1: Drawings illustrating bronchial involvement corresponding to Figures 1A and 1B.

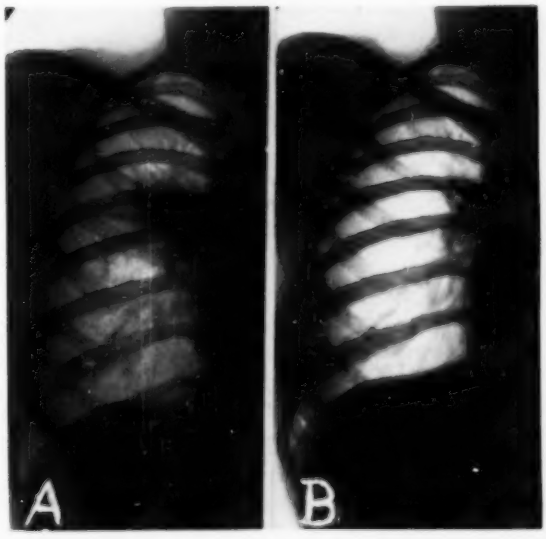

FIGURE 4, CASE 2: (A) Atelectasis of anterior segment of right upper lobe following perforation into segmental bronchus of tuberculous hilar lymph node. (B) Process in lung receding.

FIGURE 5, CASE 2: Drawings of bronchial involvement described in Figure 4.

lymph nodes in the neck. Here we find either broad perforations with acute inflammations or recidivious fistulas. Often a seemingly healed process is reactivated. We find all this in the bronchial wall as well; frequently there were large craters with more or less evident granulation, out of which caseous material could be squeezed with the tube-lip, and also in some cases boil-like eruptions with a small fistula.

Tuberculous involvement of the lymph nodes also affects the surrounding tissue, and as the bronchus is directly connected with the system of lymph nodes (being supplied by the same blood vessels and lymph passages) it suffers relatively often and we can see every variation from disrupted blood circulation to deep wall infiltration and involvement of the mucous membrane itself. To lead to a pulmonary process, however, there must in addition be a severe disturbance in the function of the bronchus. In fact a perforation together with localized destruction of the ciliar epithelium and stenosis of varying degrees leads to disturbances of ventilation and drainage, and these together with the secreted material from the caseous lymph node are ideally suited for bronchogenic dissemination and in the long run may have an important effect on the development of newly formed pulmonary foci, whereby certainly the yet unsolved problem of immunity must play a part. Except for secreting cavities and

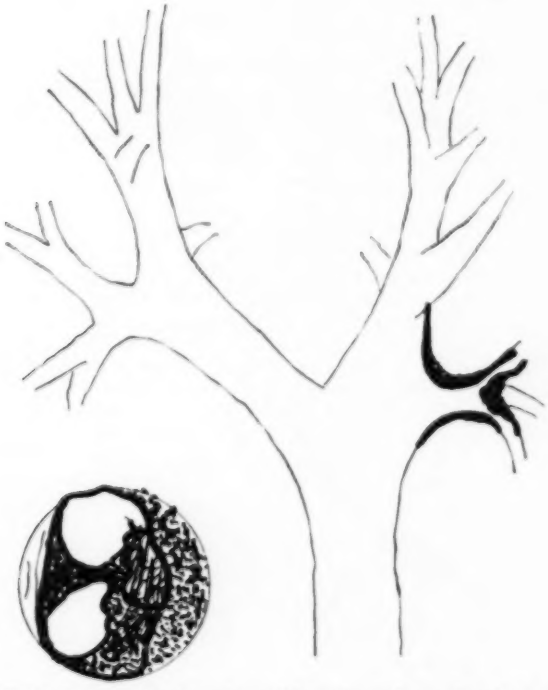

FIGURE 6, CASE 3: Schematic drawing of lymph node perforation on fork of the apical and posterior segment bronchus of the right upper lobe.

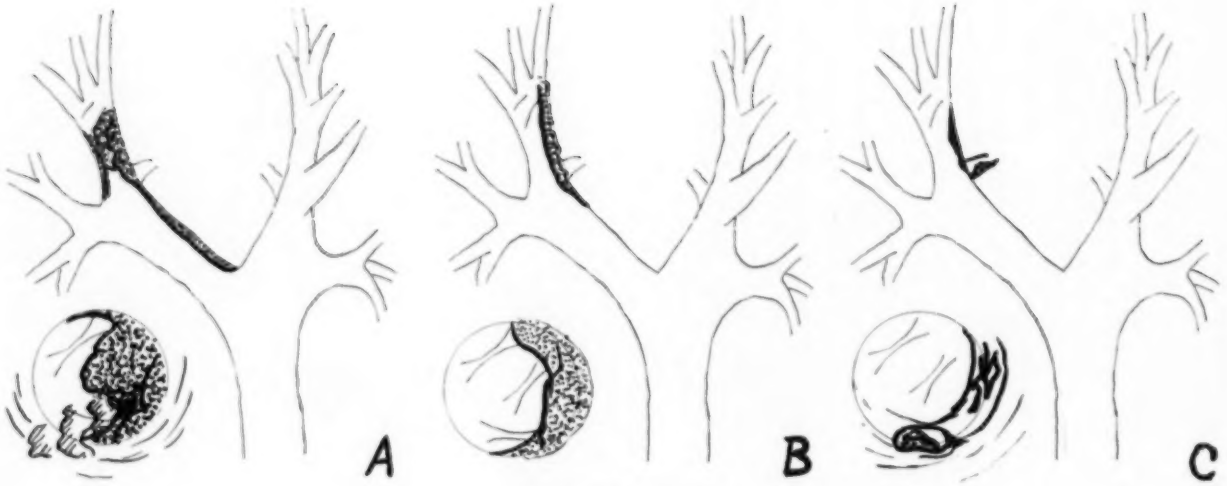

FIGURE 7, CASE 4

(A) Lymph node perforation through median wall of the left lower lobe bronchus.
(B) Healing of site of original perforation.
(C) Second perforation into apical segment bronchus of left lower lobe.

strong hemorrhages nothing is as favorable to bronchogenic dissemination. On the other hand it appears most questionable that small caseous lung foci could often lead to massive disseminations by way of the bronchi, as some clinicians and pathologists assume.

A study of the development of the processes in the bronchial wall favors this theory. After eruption of caseous material into the bronchus we could always determine a more or less pronounced granulation tendency; a further hinderance to drainage and ventilation (Figures 4 and 5). A fistula is then no more to be seen and the bronchoscopic aspect is not as clear. These changes are usually well defined, tumorlike or polypoid in appearance but can even cover larger bronchial sectors. Cicatrization may be rapid and take only a few weeks, but the fistula may remain open for many months. This was the case in a woman of 52 years of age who also developed perforation into the esophagus. The interpretation on the bronchoscopic findings alone, therefore demands greater caution; little can be said about the future course, as seemingly final cicatrization may, even after months, develop into stenosis. The typical scars are retracted and mostly anthracotic with great variations in size, but we have also observed the development of small smooth scars and circular stenosis. Localization and study of the pulmonary changes may be of help when making a diagnosis. The following three examples may be useful illustrations as they are typical:

2) This 19 year old patient had shown primary tuberculosis a year previously and then developed tuberculosis of the right hilar lymph nodes. After eight months while on streptomycin and PAS, a perforation on the anterior segment bronchus of the right upper lobe was found bronchoscopically. This, in beginning to heal, led to granulation and atelectasis in that segment. Finally, the processes both in the lung and the lymph nodes began slowly to recede (Figures 4 and 5).

3) Three months after primary tuberculosis of the right upper lobe an 18 year old apprentice developed cavernous tuberculosis of the right lung. Bronchoscopy revealed a lymph node perforation on the fork of the apical and posterior segment bronchus of the right upper lobe. With conservative treatment of rest, streptomycin and PAS, recovery was rapid. Within a few months the point of perforation had healed satisfactorily (Figure 6).

4) This 24 year old female had been successfully treated a year previously for primo-secondary tuberculosis. A lymph node perforation through the medial wall of the bronchus of the left lower lobe then developed. Eight months after this process healed, there appeared a second perforation into the apical segment bronchus of the lower lobe. This also healed with adequate treatment. The entire development was observed over a period of 18 months by eight bronchoscopies (Figure 7).

It would appear that these pulmonary changes can be satisfactorily and logically explained by lymph node perforation. However, many cases, the symptoms of which suggest such an incident but in whom there is no bronchoscopic evidence, constitute a further problem. The assumption that such evidence lies beyond the bronchoscopic field is tempting but not always satisfactory.

The examples given show that a favorable prognosis may be made for this form of tuberculosis if its origin is recognized early enough and a strict conservative treatment is undertaken. In an active process such as this, procedures necessarily leading to further disturbances of the function of the bronchus might have disastrous effects. The same is true of resection, as an operation would have to be made on an active process and the danger of a relapse remains as long as the lymph node itself cannot be touched. Poor results of active treatment are surely, in part, due to its application in cases of unrecognized perforation.

The logical therapy is rest of several months during which it is essential to stimulate the function of the bronchus by active cough in a favorable position. Expectorants may help in this respect. Endoscopically, drainage must be aided by aspiration and shrinking. Only in extreme necessity should granulation be removed as it will always recur as long as such tendency exists, and repeated action with forcep, cautery and caustics injure the functionally important remaining ciliar epithelium and often disturbs satisfactory cicatrization. Recovery from such forms of tuberculosis is definitely speeded by tuberculostatica. The combined PAS-streptomycin treatment has given good results, particularly in the bronchus. No final opinion can as yet be given on the advantages of isonicotinic acid hydrazide. Our own experiences during recent months, however, strengthen the belief in the effectiveness of this drug, particularly during the first weeks of its application.

SUMMARY

Post-primary tuberculous hilar lymph node perforation in adults is not rare. In 1,228 bronchoscoped tuberculous adults it was seen 38 times and in 81 cases the findings were regarded as residues of such perforation. The various stages of this process are described. Secondary pulmonary phthisis can apparently develop because of hilar node bronchial perforation. Early recognition of this entire process is important, as the prognosis for the changes in the lungs and bronchi is definitely favorable, if no active treatment is given. Streptomycin-PAS as well as isonicotinic acid hydrazide are beneficial.

RESUMEN

La perforación de los ganglios hiliares tuberculosos en la etapa post-primaria no es rara. En 1,228 adultos tuberculosos a quienes se hizo broncoscopia se observó 38 veces, y en 81, los hallazgos fueron considerados como residuos de tal perforación. Se describen las varias etapas de este proceso. Aparentemente, tuberculosis pulmonar secundaria, puede desarrollarse a causa de la perforación de los ganglios hiliares. Es importante que se reconozcan estos procesos completamente, puesto que el pronóstico para las alteraciones del pulmón, es favorable si no se da tratamiento activo. La estreptomicina-PAS así como la hidracida del ácido isonicotínico, son benéficos.

RESUME

La perforation de ganglions hilaires tuberculeux de primo-infection n'est pas rare chez les adultes. Au cours de 1,228 bronchoscopies pratiquées chez des tuberculeux adultes, elle fut constatée 38 fois, et dans 81 cas, él s'agissait des séquelles d'une telle perforation. Les auteurs décrivent les différents type du processus. Une tuberculose pulmonaire secondaire peut, semble-t-il, se développer à la suite de cette perforation des ganglions hilaires. Il est très important de reconnaitre précocément ce processus, car le pronostic des altérations pulmonaires et bronchiques est nettement favorable si l'on ne fait aucun traitement actif. L'action de la streptomycine, du P.A.S., aussi bien que de l'isoniazide est favorable.

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Bronchoglandular Sinus Tracts in Tuberculosis*

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There are a number of criteria for evaluating the patient with pulmonary tuberculosis and some of these are relegated to different levels of importance by local protocol or by personal equasion. The one indisputable factor which defies declassification is the presence or absence of the tubercle bacillus in the secreted material. It is still widely felt that anyone who has a positive tuberculin reaction has within themselves viable, although not necessarily pathogenic, organisms. The finest definitive diagnostic acumen is that which determines whether or not the tubercle bacilli are incarcerated or whether they are free.

No greater enigma confronts the phthisiologist than the persistently positive sputum case whose other findings are in satisfactory order. It has been the experience of all those connected with tuberculosis to observe the occasional case who has successfully run the laboratory and clinical gamut of objective tests but for one important finding—a positive sputum. This type of individual is sometimes placed in a twilight zone and is tacitly classed as some sort of carrier whose nidus of infection is beyond the pale of diagnostic support. These patients will at times gravitate to cluttered speculation and there remain to resolve themselves to what obviously is a most uncertain future.

Since tuberculosis has an affinity for lymphoid tissue it must be true that the lymphatics associated with tuberculous lungs harbor to some degree specific infection. Roentgen, postmortem and findings at operation have emphasized this universally known fact. In some of the more pronounced cases of this sort, it is difficult to postulate why these do not boil over and frequently soil the mediastinum. It is fortunate that they do not behave in the chest as they do in other parts of the body.

Sufficient emphasis has not been placed on the possibility of tuberculous nodes eroding into the bronchi. The pulmonary lymphatics are concentrated below the carina and at the proximal half of the main bronchi. Infected nodes which lie in juxtaposition to the bronchial tree will from time to time attach themselves to that structure and create a potential hazard. The accepted method of fixing the pulmonary structures in situ following postmortem examination precludes an accurate analysis of this clinical entity.

It is reasonable to assume that an infected peribronchial node which has attached itself to the bronchial tree is potentially capable of erosion into the air passages in somewhat the same manner as seen in dermal sinus tracts. Perhaps the relative rarity of bronchial erosion is the fact that the infected lymphatics have a minimum of pressure against the wall.

Except within the scope of pathology there seems to be a paucity of

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clinical information relative to bronchial sinus tracts and their prognostigative significance. An eroded node spewing forth organisms not only is noxious to the patient but prevents what otherwise might have been a clearer diagnostic vista. It is most difficult to evaluate all phases of what we hope to achieve in an individual case of tuberculosis but certainly negativity of sputum belongs at or near the top of such a list. Since the advent of modern tuberculosis therapy it has been the tendency to therapeutically hustle the patient into the charmed circle of negativity; there is nothing wrong with this concept except that if the patient does not arrive at this hoped-for destination rather promptly more consternation developes than is perhaps warranted. Being aware of the possibility of an eroded node is in order in patients who have become diagnostic puzzles.

From the eroded nodes and subsequent sinus tracts which we have observed we have concluded that there is a rather definite sequence of events. The tuberculous node probably becomes firmly adherent to the adjacent brohchial wall causing a weakness of the supporting structures. Since none of our modern medicaments have any appreciable effect on the intact diseased node, it seeks to drain itself at its weakest area and therefore erosion ensues. One such case was observed early in the process of rupture and antracotic material could be swabbed from the crater-like opening; this area was approximately 3 mm. in diameter. Practically all of our cases were under streptomycin therapy and endobronchial ulceration was kept at a minimum. The secretions noted in our cases ranged in amount from none to profuse and mucoid to purulent in character. Prior to streptomycin therapy it is quite probable that this picture represented the genesis of severe endobronchial tuberculosis of the so-called "primary" type. Most of the sinus tracts were followed by a permanent dehiscence. This fact could be explained by the protracted drainage and subsequent epitheliazation of the sinus tract. The limitation of the endobronchial disease by streptomycin administration no doubt accounts for the absence of stricture formation even in the presence of a fairly large crater at the onset.

The question has been posed many times as to how far the tubercle bacilli must be eradicated before the patient may be considered clinically well. It is not unusual for discharged patients to have an occasionally positive sputum and I would hazard a guess that if all former patients had a daily sputum test the results would, if taken seriously, create a tempest which would change our modern tuberculosis programs in all directions. A well walled-off peritracheal node which lies at the distal end of a bronchoglandular sinus tract and which is the seat of occasional tubercle bacilli probably is of considerably less import than if the parenchyma of the lung was the source.

The bronchoscopic appearance depends to a large extent on the time element. The earliest case noted at this sanatorium had the appearance of a miniature volcano with the vertex presenting a crater in which was noted considerable granulation tissue. Even though the patient was in the early twenties tumor was suspected and a biopsy was taken; this showed

only granulation tissue. Since there was a rapid resolution under streptomycin therapy no further material was taken. It is not uncommon in endoscopy to encounter difficulty in establishing a diagnosis by biopsy and it is no reflection on the pathologist if a definite diagnosis is not made. Unless there is a clear-cut and visible tumor mass present we feel that all ulcerative and granulomatous lesions of the bronchi and trachea should be treated as tuberculous if the particular case be a proved one of pulmonary tuberculosis. Perhaps this does not follow the older tenents but it is justifiable in the light of the rapid and favorable response to antimicrobial therapy. Since our patients are routinely given a repeat bronchoscopic examination if there is any abnormality present, we are of the opinion that this regime is to the best advantage of the patient. A biopsy of the trachea and bronchi, even in the best of hands, is not without hazard and we feel that a therapeutic test with streptomycin alone or in combination is in order. It goes without saying that all lesions of the air passages should forthright have a careful study made of the lungs before biopsy is taken. This certainly is by no means anything original but is only for emphasis to prevent surgical mayhem in which the operator is looking at secondary and overlooking primary tuberculosis.

Under the influence of streptomycin and other forms of therapy the originally erupted node will almost always subside and leave a shiny-lipped circular opening with a diameter of 1 to 2 millimeters. Unless the mucosa is free from secretions at the time of examination a residual sinus tract may be easily overlooked. The opening may or may not be secreting at the time of examination but since it leads into a field of undetermined pathology its presence should always be considered culpable.

It has been known for some time that tuberculosis of solid organs responds hardly at all to streptomycin or other forms of medical therapy. This fact is probably accounted for by the fact that enteral medicaments are unable to penetrate the barrier of fibrosis and endarteritis. It naturally follows that infected nodes sustain tubercle bacilli which are fortified to some degree against outside influence and that removal of these nodes is the surest recourse to recovery.

SUMMARY

The importance of bronchoglandular sinus tract formation in tuberculosis is stressed. These are important in making a diagnosis and also in outlining future therapy. It is important for the future of the patient to know whether positive secretions are coming from an infected gland or whether these are originating in the parenchyma of the lung. Since these sinus tracts are usually permanent, they are expected to drain intermittently and will cause apprehension both to the patient and the physician if the material includes tubercle bacilli.

RESUMEN

Se hace énfasis sobre la influencia que en tuberculosis tiene la formación de trayectos bronco-ganglionares. Estos son importantes al hacer el diag-

nóstico y también al planear la terapéutica. Es importante para el futuro del enfermo, saber si las secreciones baciliferas provienen de un ganglio infectado o del parenquima pulmonar. Puesto que estos trayectos son habitualmente permanentes, es de esperarse que canalicen intermitentemente y causen así aprehensión tanto por parte del enfermo, como del médico si el material excretado contiene bacilos.

RESUME

L'auteur insiste sur l'importance des fistules bronchoganglionnaires dans la tuberculose. Leur existence permet de faire le diagnostic, et ainsi d'esquisser la thérapeutique future. Il est important pour l'avenir du malade de savoir si les sécrétions chargées de bacilles proviennent d'une glande infectée ou si elles tirent leur origine du parenchyme pulmonaire. Comme ces fistules sont généralement permanentes, il faut s'attendre à ce qu'elles soient l'objet d'un drainage intermittent, et que si on constate dans leurs sécrétions des bacilles de Koch, ce soit là l'objet de craintes pour le malade et le médecin.

Acute Bronchopulmonary Suppuration: Therapy with Endoscopic Application of Oleaginous Penicillin*

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For purpose of discussion the entity of bronchopulmonary suppuration must be better defined anatomically. With the advent of improved knowledge and standardization of the bronchopulmonary segments[1] we may assume that the segment be considered the pathological unit of suppurative disease in the lung. Larger areas of pathology are made up of two or more segments up to the lobar aggregate of the component segments. The peculiar anatomical localization of bronchopulmonary suppuration, since it starts with blockage of a segmental bronchus and involves a definite segment of the lobe, makes this concept fairly acceptable and practical. The radiographic as well as the bronchoscopic manifestations of this entity both permit the possibility of using the segment as the pathological unit of suppurative disease of the lung.

Again, for purpose of better definition and in consonance with the expressions in the literature,[2-7] the various disease states which have been rather loosely described as "unresolved pneumonia," "middle lobe syndrome," "drowned lung," "residual interstitial pneumonia," "partial atelectasis," "obstructive pneumonitis," "fibrous pneumonia," "parenchymal fibrosis," "focal parenchymal fibrosis," "chronic suppurative pneumonitis," etc., may all be fitted into the segmental pattern. These are, in all probabilities, originally due to disturbances of the normal function of the segments secondary to intrinsic or extrinsic bronchial block; and therefore different pathological manifestations of bronchial block.

The pathological changes following bronchial obstruction have been fairly well studied both clinically and pathologically[2,4-10] and the following sequellae of such block well accepted in the literature:

1) Blockage occurs from retained exudates, transudates, or aspirates (liquids or solids). Rapid absorption of the air distal to the block occurs with creation of a vacuum which retains the viscous mass. The absence of the normal air cushion distal to the block impedes the normal expulsive efforts of the lung to free the plug. Retention of the mass in time dulls the receptors which initiate the cough reflex. The cilia in turn become powerless since the mass may be too tenacious for their efforts at removal; and the spiral musculature which molds and pushes the mass cephalad

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*Presented before the Second International Congress on Diseases of the Chest, American College of Chest Physicians, Rio de Janeiro, Brazil, August, 1952.

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All the instruments mentioned in this paper are available from the George P. Pilling & Sons Company, 3451 Walnut Street, Philadelphia, Pennsylvania, to whom the author has given the specifications for their manufacture.

soon becomes exhausted for the same reason. Unless the plug is removed and the normal function of the segment re-established, we enter the first phase of bronchopulmonary segmental pathology—*atelectasis*. This phase may be considered reversible since the pathological changes are absent or mild.

2) Once the normal respiratory function of the segment is altered by block, the retained semi-liquid mass inspissates and coagulates in the bronchus and alveoli to make the segment fairly solid and thus further decrease its ability to regain its function. Pressure from the contiguous healthy segments closes off or impedes the normal lymphatic and capillary circulation and at the same time cuts down or nullifies the venous return with creation of passive congestion and transudation of fluids. Now even the normal defense of phagocytosis and lymphatic absorption of the offending mass is no longer operative. The segment becomes, to all intents and purposes, a dead unit which in time may undergo *fibrosis* or *carnification* never to recover its respiratory function.

3) If there is a predominance of the proper organisms; or if the destructive processes to be described are fulminating, *acute abscess* may form. In cases where the body survives the toxemia and self-drainage is established a *chronic lung abscess* results.

4) The pathological process in the segment may alter the mucosa resulting in edema, erosion, ulceration, granulation, and eventually destruction of the muscularis, cartilage, and elastic tissue with resulting ectasia. Modified epithelium relines the damaged bronchus with the establishment of *irreversible bronchiectasis*.

In view of the pathological sequence of events just described, it would appear that the entities presently recognized by various terms and syndromes could be grouped into three distinct categories which center about the concept of the bronchopulmonary segment as the initial focus and pathological unit of bronchopulmonary disease:

1) *Acute suppurative segmental bronchopneumonitis, obstructive in type.* (Acute suppurative atelectasis, acute bronchopulmonary suppuration, acute abscess.)

2) *Chronic fibrous segmental bronchopneumonitis, obstructive in type.* (Segmental fibrosis, carnefication, chronic atelectasis, chronic interstitial pneumonitis.)

3) *Chronic suppurative segmental bronchopneumonitis, obstructive in type.* (Chronic abscess, bronchiectasis, chronic suppurative pneumonitis.)

Since this paper is primarily concerned with the therapy of the acute phase of bronchopulmonary suppuration, no attempt will be made to further discuss the chronic phases of this entity except to state that its therapy is in the realm of extirpative surgery.

The Clinical Phase of Acute Suppurative Segmental Bronchopneumonitis

Clinically acute suppurative segmental bronchopulmonary pneumonitis is an acute illness which is characterized by chills, fever of the septic type, cough, expectoration, pleuritic pain, dyspnoea and hemoptysis which may

be either frank or characterized by streaked spittles. Malaise and the usual concomitants of systemic toxemia are also present. Pleuritic pain, dyspnoea, and hemoptysis may not be present. In some patients the constitutional symptoms may be absent and the entity discovered on a routine film following acute episode of lower respiratory infection. The physical signs may be entirely absent unless the segment involved lies superficially, when dullness and deep-seated rales are noted. At times an associated effusion may be present. Leukocytosis is usually found and in patients with a paucity of symptoms the count may even be normal. The sedimentation rate is usually accelerated; yet it too may be normal in patients with few symptoms. When this is the case it is assumed that the block is intermittent and the toxemia present only during the intervals of block. The x-ray picture is characteristic and present in all cases. This shows a constant opacity confined to a bronchopulmonary segment. Gravitational forces do not seem effective in confining the process to the dependent portions of the lungs as it may be commonly seen in the upper lobes. No segment may be specifically spared. Oblique and lateral studies must be made to supplement the routine film for proper evaluation as the segment must be viewed in its proper anatomical and dimensional relationship to the rest of the lung for proper diagnosis and identification.

The bronchoscopic picture is needed to round out the diagnosis. This may show pus oozing from the involved bronchus; though on occasions no pus is seen and seriatim aspiration of each segmental bronchus in the area must be made before pus can be detected. In the cases studied the mucosa was almost always more or less normal except for the visible excessive purulent secretions which were seen on the surface. With the exception of the pus the bronchoscopic picture cannot be considered pathognomonic. On Papanicoloau stain the aspirated secretions show numerous polymorphonuclears in their normal state or exhibiting various stages of degeneration. Normal cellular components such as ciliated cells and macrophages were frequently seen in small numbers. On direct smears the secretions were found relatively free of organisms though some cases presented numerous pneumococci.

The Rationale of Endobronchial Application of Oleaginous Penicillin.

Interest in the present method of treatment evolved with the discovery that antibiotics could be safely introduced into the lungs by aerosol techniques. This new portal of therapy became rather wide-spread since it could be used at home by the patient and was recommended for practically any bronchopulmonary infection for either definitive or palliative therapy. Careful consideration was given this technique for possible use in focal bronchopulmonary suppurations but the conclusion reached that there were several distinct disadvantages to the method for these purposes. First it was felt that diagnostic bronchoscopy was in order to definitely make the diagnosis and rule out other pathology such as a foreign body or neoplasm. Secondly it was felt that since acute bronchopulmonary suppuration presupposed a focus with a plugged bronchus and absent or

deficient respiratory function of the segment, the introduction of an antibiotic nebulum in the respiratory tract permitted very little of it to enter the diseased area.[11] Again, on the assumption that absorption occurred from the entire vascular pulmonary bed, very little of the blood-borne antibiotic would concentrate in the diseased segment because of its relative avascularity. It was decided that this was the reason for failure of the parenteral or aerosol administrations of antibiotics in the cases studied.

It was noticed that lipiodol whose viscosity closely approximates that of penicillin in oleaginous medium could be introduced bronchoscopically into selected bronchi and would remain in the normal or even abnormal lung for long periods of time up to six months. The use of oleaginous penicillin in the same manner for focal therapy immediately suggested itself. The next step was to test the tolerance of the bronchi and alveoli to its instillation. This was done in the human subject with very little quantities and the amount gradually increased to three and four cubic centimeters with no untowarded local or systemic results. The control patients were followed with x-ray studies as well as clinical observation. The original studies were conducted on known bronchiectatics and later on cases of bronchopulmonary suppuration. It may be stated parenthetically that this procedure in well-established bronchiectasis has been found useful in thinning the secretions, abating the symptoms, and preparing patients for surgery. Some patients experienced a marked increase in weight and freedom from toxemia but long-range study soon limited its use only to preoperative preparation of the poor-risk patient. An interesting complication was the development of a rather severe penicillin reaction of an urticarial type two weeks following endobronchial instillation.

At body temperature penicillin in oil retains a fair viscosity and appears to remain in situ even after cough with very little loss. To detect the drug in the spittles, the preparation was dyed with Sudan III which gave it an orange color. Very little appeared in the sputum. At times none was noted in spite of the fact that the patient was alerted to watch for the orange discoloration. Bronchoscopically it was noted that if the instillation is made deep into the involved bronchus, the preparation cannot be seen oozing from the area even after the lapse of some time.

Method of Application of the Penicillin and the Instruments Used:

To facilitate the introduction of the penicillin a special applicator was designed which fitted a standard luer-lok syringe. The length was 50 cms. The tip was of the velvet eye type (Jackson) to render it atraumatic. The diameter was about 2 mm. The proximal end was fashioned with a bayonet curve so that unimpeded vision could be had to accurately place the tip. For "around the corner" work a second applicator was designed which had the same general characteristics except that it was fitted with a curved spiral tip. Bronchoscopy was under local anesthesia by a method developed by the author.[12] It was discovered that a 2 cc. syringe was better than a 5 or 10 cc. since the latter "froze" when used with oleaginous penicillin.

Case 1, Figures 1-5: (Rev. D.) Acute lung abscess with cavitation of two weeks duration. Treated since onset with terramycin. Involvement of the anterior bronchopulmonary segment of the right upper lobe.

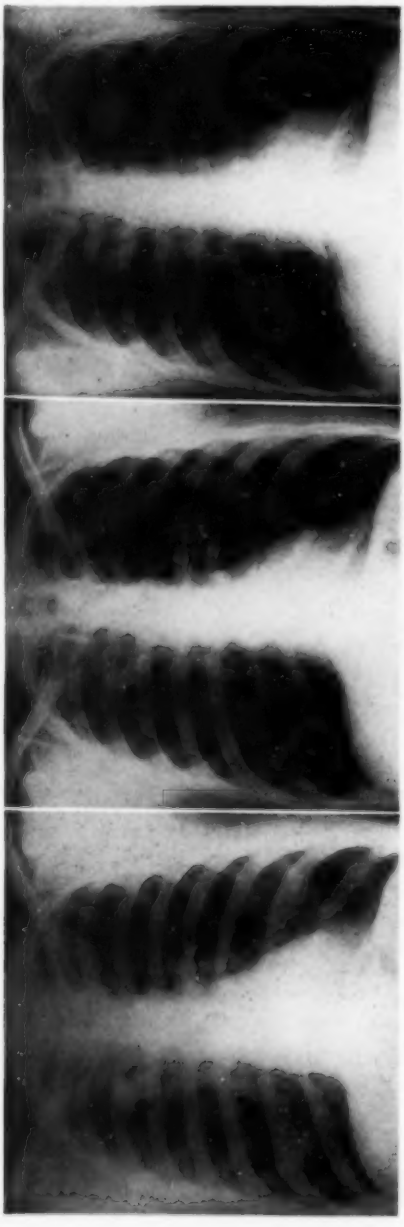
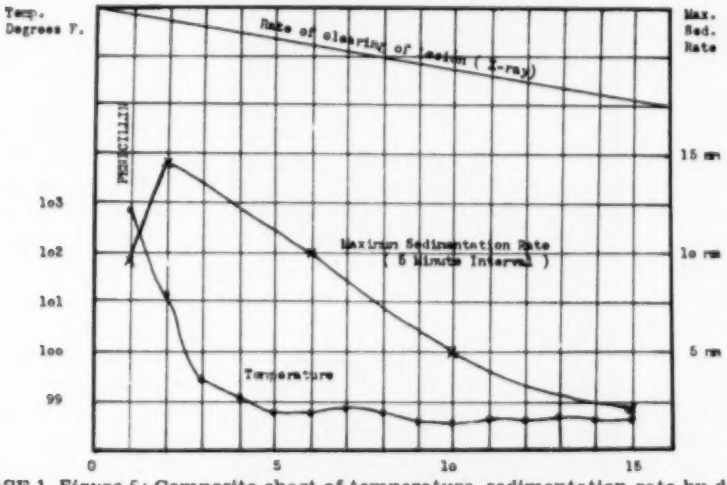


FIGURE 1 FIGURE 2 FIGURE 3

CASE 1, *Figure 1:* Film taken just prior to the endobronchial instillation of a single dose of 600,000 units of oleaginous penicillin.—*Figure 2:* Two days later, showing the decrease in the size of the abscess cavity and the parenchymal inflammatory mass.—*Figure 3:* Four days later, showing closure of the cavity and marked decrease in the parenchymal reaction.

During the bronchoscopy the area under suspicion is carefully inspected and at times the bronchus concerned can be readily identified by the pus which oozes from its orifice. However, this is not always the case and each visible segmental bronchus must be aspirated seriatim until pus is obtained. On occasions pus was obtained from several adjacent bronchi in which case instillation was made in each as it was difficult to tell whether pus had been aspirated from a diseased segment into a normal segment or whether two segments were involved. For aspiration a special specimen collector was designed which permitted collection of very small quantities

CASE 1, *Figure 4:* Sixteen days later, showing only fibrotic elements with complete disappearance of the abscess cavity.



CASE 1, *Figure 5:* Composite chart of temperature, sedimentation rate by days and the relative clearing rate of the lesion on x-ray film following endobronchial penicillin therapy.

Case 2, Figures 1-3: (M.M.) Acute bronchopulmonary suppuration of two weeks duration with no prior therapy. Process confined to the medial bronchopulmonary segment of the right middle lobe.

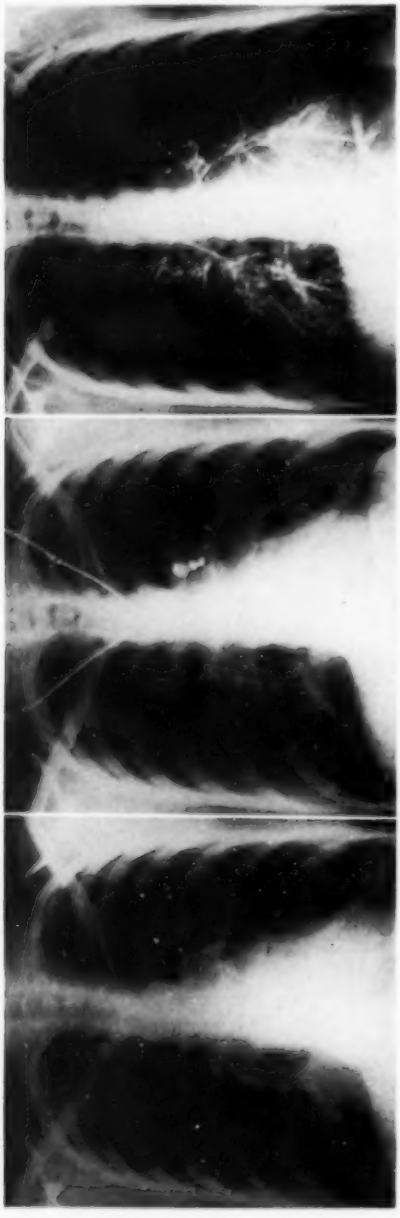


FIGURE 1 FIGURE 2 FIGURE 3

CASE 2. *Figure 1:* Initial film taken prior to endobronchial instillation of 900,000 units of oleaginous penicillin. — *Figure 2:* Eight days later, showing almost complete disappearance of the suppurative process. — *Figure 3:* Bronchogram done at the same time showing questionable dilatation of the area involved in the suppurative process.

of pus. Coarse collectors are not recommended as they will not enter deeply into the bronchi and pus will be lost in the collecting system and cannot be easily handled for special studies. Once pus is obtained, the bronchi is identified for the introduction of the penicillin. The amount of penicillin was arbitrarily chosen and usually amounted to 2 or 3 cc. representing 600,000 to 900,000 units. Under direct vision the tip of the applicator is placed into the bronchus and gently introduced until it stops. No pressure must be used as the structures at these levels are delicate and perforation may occur. The patient is asked to take deep breaths and the penicillin slowly introduced. Haste will result in regurgitation of the preparation from the bronchus. Slow introduction permits it to be "breathed" into the segment and aspirated into the diseased area as the segment has partially recovered its respiratory function following the removal of the pus. When the syringe is empty, the full dose has not been introduced since about 1 cc. remains in the applicator proper. The syringe is disconnected, filled with air and the air gradually injected. This process is repeated several times so that the residual penicillin in the applicator is also introduced thus assuring the patient of the full intended dosage.

Material Studied:

The material studied consisted of 10 patients with bronchopulmonary suppuration of the segmental type. One had an associated basal serosanguinous effusion which complicated the primary diagnosis. Another had a typical segmental lesion which differed from the others in that the mucosa was an intense crimson red and very velvety. Routine smear showed that the secretions teemed with tubercle bacilli. The acute phase of this patient as well as the results with endobronchial penicillin paralleled the course of the others and hence was included in the series. It is interesting to note that the lesions occurred in the left lower lobe. It is further interesting to note that suppuration in endobronchial tuberculosis may mask the underlying diseases and shows the importance of routine smear for tubercle bacilli in all patients.

The acute symptomatology of most of the patients began and persisted from one week to four weeks prior to bronchoscopy and penicillin instillation. A definite history of specific antecedent disease was not at all characteristic. All had been treated for such indefinite entities as "colds," "bronchitis," "virus infection," "grippe," etc. All the patients, however, had had the benefit of thorough treatment with penicillin, aureomycin, terramycin, etc. Several had penicillin aersol. Several of the patients gave a history of repeated attacks of "pneumonia" or "bronchitis." Weight loss was characteristic of the majority during the acute phase of the disease. Constitutional symptoms varied from temperatures of 104 degrees F. with associated chills and signs of sepsis to mild pyrexia with few symptoms except cough and expectoration which appeared to be constantly present in all cases. About 50 per cent of the patients looked and were rather ill. Hemoptysis was present in four and varied from frank bleeding to streaked sputa. Accelerated sedimentation rates were present in almost all cases

though some were normal. Leukocytosis was seen in seven cases. X-ray film studies showed lesions characteristic of bronchopulmonary suppuration of the segmental type in all cases. These lesions were located anatomically as follows: Right upper lobe 3, right middle lobe 3, right lower lobe 2, left upper lobe 0, left lower lobe 2.

Results:

It was quite striking to see the almost immediate improvement both in the temperatures as well as the cough and expectoration in each of the patients thus treated. At times a rather dramatic result was noted in

Case No. 3, Figures 1-4: (M.K.) Acute bronchopulmonary suppuration confined to the anterior bronchopulmonary segment of the right upper lobe of one week duration. Patient on parenteral penicillin therapy.

FIGURE 1 FIGURE 2

CASE 3, *Figure 1:* Film taken at the time parenteral penicillin began, 300,000 units daily.—*Figure 2:* Film taken after 10 days trial at parenteral penicillin. Note increase in the size of the lesion. Endobronchial penicillin begun on this date—one instillation of 900,000 units.

FIGURE 3 FIGURE 4

CASE 3, *Figure 3:* Film taken seven days following the instillation of endobronchial penicillin. Note the marked change in the size of the lesion and reappearance of radiolucency of the area involved.—*Figure 4:* Film taken three weeks later. There is almost complete resolution of the original lesion.

from one to two days. In most cases the temperature dropped to almost normal on the day following the endobronchial penicillin instillation. Three cases had a slow temperature drop which took a week to become normal. Two of these latter cases required a second aspiration and penicillin instillation. The morbidity as judged by the temperature was never longer than one week in any of the sieres. X-ray film evidence showed clearing of the lesions in one week in most cases; in a few it took two weeks and in the more severe, three weeks. The reversion of the sedimentation rate to normal grossly paralleled the time required to clear the x-ray picture. The amount of secretions or their type apparently had no bearing on the severity of the lesion. One patient with 15 cc. of puro-sanguinous secretions had a clear x-ray film in one week and the acute symptoms subsided in two days. On the other hand a patient with only 2 cc. took one week before she was temperature free and the x-ray film cleared in three weeks. Follow-up bronchograms were done on six of the series and definite mild segmental bronchiectasis diagnosed in one.

Discussion

The chain of events which follows obstruction of a segmental bronchus is due to disturbance of the normal expulsive and excretory forces of the segment. Pathological increase in the size of the lesion is additive by involvement of contiguous segments by the same secretions of the original focus. The causative factor therefore must be considered one of mechanical block with the cause of the obstruction an exudate, transudate, or aspirate. Extrinsic pressure by glandular enlargements has been fairly well proved in the case of the middle lobe but the same cannot be said of other areas. Bronchostenosis as an etiological factor is acceptable theoretically but the fact remains that in the acute cases it is rarely, if ever, seen bronchoscopically and in pathological specimens may well be due to the end result of the suppurative process.

As can be readily seen the source of the offending semiliquid mass in the segmental bronchus will be rather difficult to determine since any of the following may be operative: Postnasal drip (sinusitis); exudates secondary to any of the lower respiratory infections; foreign bodies that are not removed early; residual clots in the bronchi following pulmonary hemorrhage; inspissated secretions following the use of atropine and heavy sedation; lipoid products following the use of nose drops.

A fundamental question to be settled is whether or not we are justified in the large scale use of cough depressants on the theoretical and practical basis that all coughs are to be stopped. Certainly we know that anatomically the tracheobronchial tree is a cul-de-sac with a countergravitational pathway for excretion; we are aware that infections in this area are characterized by a bronchorrhea with secretions of varying viscosities; and again we are familiar with the end results of retention and block in the bronchial tree. And yet, in spite of all this fundamental knowledge, the practice of medicine in the realm of cough control goes counter to the basic principle that these secretions must be removed by the normal

defense mechanisms of excretion inherent in all lungs. We routinely prescribe drugs which definitely depress the cough reflex, suppress the excretory mechanisms at the segmental level, and even inspissate the secretions! In children especially is the habit of cough elimination dangerous since the viscosity of the secretions is the same as in the adult and yet the bronchial lumina are proportionately much smaller.

Early diagnosis of acute suppurative segmental bronchopneumonitis and its treatment will prevent the chronic sequellae[3,6-8] of this entity which is responsible for so large a proportion of all chronic pulmonary disease.

SUMMARY

1) The clinical entity of acute bronchopulmonary suppuration is better classified as *acute suppurative segmental bronchopneumonitis, obstructive in type* since the primary focus is the bronchopulmonary segment which may be considered the pathological unit. This concept is also in harmony with the radiological as well as the bronchological aspects of this disease.

2) Antibiotic therapy via parenteral as well as aersol route has not been particularly effective in the author's experience in the treatment of the acute phase of this disease.

3) A new method of endobronchial instillation of oleaginous penicillin directly into the segmental bronchus involved is described as are the instruments required for this procedure.

4) A series of 10 patients with acute suppurative segmental bronchopulmonary pneumonitis, obstructive in type, in which this method was used with rather dramatic results is reported.

5) The method is also recommended for "poor-risk" patients of chronic suppurative bronchopneumonitis prior to definitive surgery.

6) Early therapy of acute suppurative segmental bronchopneumonitis, obstructive in type, with endobronchial penicillin is a powerful prophylactic method for avoiding the chronic sequellae of this entity.

RESUMEN

1) La entidad clínica de la supuración aguda broncopulmonar, se clasifica mejor como bronconeumonitis supurativa segmentaria de forma obstructiva, puesto que el foco primario es al segmento broncopulmonar que puede ser considerado como la unidad patológica. Este concepto está también en armonía con los aspectos radiológicos, así como el broncológico de la enfermedad.

2) El tratamiento por los antibióticos por vía parenteral así como por los aerosoles, ha sido especialmente efectivo según la experiencia del autor en esta enfermedad aguda.

3) Un método nuevo de instilación de penicilina oleaginosa directamente dentro del bronquio segmentario comprometido se describe, así como los instrumentos requeridos para este propósito.

4) Se refieren los casos de diez enfermos con bronconeumonitis aguda supurativa segmentaria de forma obstructiva, tratados con este método con resultados espectaculares.

5) El método es también recomendado para los enfermos considerados como "malos riesgos" de bronconeumonitis supurativa aguda, antes de

emprender la cirugía.

6) El tratamiento precoz de la bronconeumonitis aguda supurativa segmentaria de forma obstructiva, por medio de la penicilina endobronquial, es un método profiláctico para evitar las secuelas crónicas de esta enfermedad.

RESUME

1) La suppuration bronchopulmonaire aigue serait mieux désignée comme bronchopneumonie aigue suppurative segmentaire, à type obstructif. Le foyer primitif et anatomiquement défini est en effet le segment bronchopulmonaire. Cette conception est également en accord avec les aspects radiologiques et bronchologiques de l'affection.

2) Selon l'expérience de l'auteur, la thérapeutique antibiotique par voie parentérale ou par aérosols, n'a pas été particulièrement efficace dans le traitement de la phase aigue de cette affection.

3) L'auteur décrit une nouvel le méthode d'instillation endobronchique de pénicilline huileuse, ainsi que les instruments utilisés pour cette technique.

4) L'auteur rapporte les observations de 10 malades atteints de bronchopneumonie suppurative segmentaire à type obstructif, chez lesquels ce traitement fut appliqué avec des résultats assez impressionnants.

5) Le procédé est également recommandé chez les malades moins dangereusement atteints, porteur de bronchopneumonie suppurative chronique avant qu'ils ne subissent l'intervention chirurgicale.

6) Le traitement précoce de la bronchopneumonie aigue suppurative segmentaire à type obstructif avec la pénicilline endobronchique est une méthode efficace pour assurer la prophylaxie des séquelles chroniques de cette affection.

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Erythema Nodosum and Hilar Lymphadenopathy*

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Erythema nodosum is generally regarded as a "non-specific inflammatory reaction of the skin to a variety of bacterial, toxic, and chemical agents,"[1] usually associated with an acute febrile illness, and often with joint pains and malaise. Not infrequently erythema nodosum is associated with pulmonary hilar lymphadenopathy; therefore, it must be considered in the differential diagnosis of patients with enlarged hilar shadows. This fact does not seem to be generally known, and since there are obvious practical considerations involved, the authors consider it worthwhile to review the thoracic manifestations of the disease, and briefly to present four cases.

Clinical Features:

In the typical case of erythema nodosum, there is a febrile onset with temperature elevations to 100-102 degrees F., associated with, or followed in a few days by, the appearance of painful nodular erythematous lesions on the shins, and sometimes on the forearms, buttocks, chest and elsewhere. These nodules vary in size from a few millimeters to five or six centimeters in diameter. They are not fluctuant and do not suppurate. The overlying skin is smooth, shiny, and usually a rose-red or purplish-red color or even fiery red. The nodules are often tender and painful. After a few days to several weeks, they slowly subside, leaving brownish pigmented areas which slowly fade.

The patient often complains of painful swollen joints during the acute stage of the illness. An interesting and not infrequent finding is cardiac involvement, manifested by such electrocardiographic changes as prolonged A-V conduction or flattening or inversion of T-waves.[2] The heart may appear dilated temporarily by roentgenography, but so far as is known, there is no persistent heart damage.

Pathology and Pathogenesis:

The skin lesions show dilatation of the capillaries, extravasation of serum, leukocytes and erythrocytes into the surrounding tissues, and later disintegration of the red blood cells which gives the characteristic color of the lesion. The changes are those of a non-specific inflammatory reaction only, regardless of the etiology.

The pathogenesis is unknown, though the lesions are thought to represent a peculiar allergic response to various agents. In cases of erythema nodosum with lymphadenopathy associated with sarcoidosis or tuberculosis, the involved lymph nodes show the typical pathology of the underlying disease. The authors have not encountered reports of examinations of the

*Read at the Northwest Regional Meeting of the American College of Chest Physicians, Vancouver, B. C., on November 14, 1952.

hilar nodes in other conditions associated with erythema nodosum or in erythema nodosum per se, and are not aware of any autopsy reports of patients with erythema nodosum and cardiac involvement who have died in the acute stage of the disease.

There are many other questions about erythema nodosum which remain unanswered, for example: why do the skin lesions occur where they do; what accounts for the varying incidence and etiology in different parts of the world; why do the lesions tend to recur in up to 10 per cent of patients; why is there a seasonal incidence with more cases in the spring; and why do hilar nodes tend to be enlarged, whereas the superficial nodes generally are not?

Etiological Agents:

Since 1798, when the term "erythema nodosum" was introduced and the skin lesions first described, a great volume of medical literature has accumulated. Until the 1930's, the majority of writers considered erythema nodosum to be a specific entity, though its association with tuberculosis was known as early as 1870. Some considered this combination to be most common in childhood and rare in adults. Scandinavian observers especially have been convinced that erythema nodosum is chiefly a sign of early tuberculosis, probably an allergic manifestation. It has been noted, for example, that a positive tuberculin test may appear for the first time when erythema nodosum develops, or at least soon afterwards. Various Scandinavian reports give tuberculosis as the etiology in 50 to 95 per cent of the cases, but British and American authors consider tuberculosis to be less important than other infectious diseases.

In the United States, upper respiratory infections, especially those due to beta-hemolytic streptococci, seem to be the commonest etiological factor in erythema nodosum. Some argue that erythema nodosum is often a manifestation of rheumatic fever, but the frequency of this combination has probably been exaggerated because of the non-specific joint and heart manifestations which sometimes occur together with erythema nodosum.

Other infections have been reported to precede erythema nodosum, for example, granuloma inguinale, dental infections, leprosy, fungus infections, chronic ulcerative colitis, upper respiratory infections and acute gastroenteritis.

Erythema nodosum has apparently been precipitated by the ingestion of various drugs and toxic agents, including iodides, bromides, salicylates, sulfonamides, thiouracil, antibiotics and heavy metals.

Sarcoidosis has been reported in several instances, as in two of Lofgren's[2] 178 cases of erythema nodosum, where of six patients with bilateral hilar lymphadenopathy and miliary pulmonary infiltrations, two had sarcoidosis.

Coccidioidomycosis is in a special category, because of its endemic character in certain areas. In an epidemic occurring in a group of 75 soldiers, Goldstein and McDonald[3] reported that erythema nodosum developed in 19 per cent. Hilar lymphadenopathy and parenchymal pulmonary infiltrations are commonly seen in the chest films of patients with cocci-

dioidomycosis and erythema nodosum, making up the classical picture of "Valley Fever".

Syphilis has been reported in association with erythema nodosum but is probably not causally related. It is interesting that serologic tests for syphilis are often temporarily falsely positive in cases of erythema nodosum, particularly in those associated with acute respiratory infections.

Erythema Nodosum and Hilar Lymphadenopathy:

The first report of pulmonary hilar lymphadenopathy in erythema nodosum appears to be that of Ernberg,[4] who in 1921 found enlarged hilar shadows in the chest films of 30 of 39 children with erythema nodosum. Of 31 of these children who were followed, 13 later developed tuberculosis.

In 1937, Spink[1] reported 133 cases of erythema nodosum in the United States, of whom 48 had chest films. Three of these showed hilar lymphadenopathy, an incidence of about 6 per cent.

In 1941, Paul and Pohle[5] studied 42 patients with erythema nodosum, of whom 20 had chest films. Nine of these showed hilar enlargement, slight in three cases and moderate in six. Two of these nine cases had a definite tuberculous etiology. In the same year, King[6] stated that erythema nodosum may give changes in the chest film indistinguishable from those of sarcoidosis, and that both diseases should be thought of in patients with bilateral hilar lymphadenopathy, especially if the tuberculin test is negative. Kerley[7] in 1942 reported 12 cases of erythema nodosum with hilar lymphadenopathy, bilateral in 10 instances, where sarcoidosis was present in two of the patients.

An incidence of about 10 per cent of bilateral hilar enlargement was reported in 354 cases of erythema nodosum by Skiold[8] in 1945. Apparently none of his patients showed evidence of active pulmonary tuberculosis though 91 had evidence of previous tuberculous infection. A much higher incidence of enlarged hilar shadows in erythema nodosum is mentioned by Keil,[9] who says that it occurs in 50 to 90 per cent of children with erythema nodosum. In Lofgren's[2] series of 178 cases of erythema nodosum previously mentioned, 102 showed unilateral hilar lymph node enlargement and 30 bilateral lymphadenopathy. When tuberculosis was the etiological agent (104 cases), the adenopathy was unilateral in 86 per cent and bilateral in only 9 per cent. In two other series, the incidence of enlarged hilar nodes in erythema nodosum appears to be about 20 per cent.

In 1951 Johnson et al.[10] of the Mayo Clinic, reporting on the subject of erythema nodosum with pulmonary hilar adenopathy, considered that this probably represents an entity in itself. Of the 100 cases of erythema nodosum they reviewed, nine had pulmonary hilar lymphadenopathy. This may not be the true incidence, since only patients who had chest roentgenograms as well as the typical cutaneous lesions were considered. In their series, females outnumbered males by three to one though the opposite ratio has been noted by others. Most of their patients were adults. It is interesting that the disease had a chronic course, i.e. six to 12 months in 4 per cent, and was recurrent over a period of years in 15

per cent. In the etiology of their cases, upper respiratory infections outnumbered miscellaneous infections. There was a positive tuberculin test or clinical evidence of tuberculosis in four of the 100 patients, and in 15, sensitivity to sulfonamides or bromides was present. However, there was no disease other than erythema nodosum apparent in 30 of the cases.

In the nine patients with associated pulmonary lymphadenopathy, the latter was bilateral in eight patients and unilateral in one, and no cause other than erythema nodosum could be found to explain it. In four of the five with hilar lymphadenopathy who were followed, enlarged hilar shadows disappeared after the regression of the skin lesions. The roentgenogram had returned to normal within several months, except in one instance where hilar enlargement persisted for 20 months.

It appears from the literature that only symptomatic treatment has been offered, for example, salicylates for fever and joint pains, because of the presumably self-limited nature of the disease. It is quite likely that a number of cases of erythema nodosum associated with bilateral mediastinal adenopathy have been mistaken for lymphomas and have been given deep roentgen therapy, of course with excellent results!

We have seen several patients with hilar lymphadenopathy due to erythema nodosum in recent years, and four illustrative case reports are presented.

Case 1: (Mr. T.S.) This 48-year-old male had "the flu" for several days in February 1951, followed by fatigue. Late in March, he began to have night sweats and low-grade fever. Aureomycin was prescribed, and one day later there was considerable swelling of the feet and ankles which persisted for over a month. Late in April, he developed red painful nodules over the lower legs. Mild dull nonpleuritic right lower anterior chest pain was present for a few days at this time.

Physical examination on May 7, 1951 showed the typical lesions of erythema nodosum over the tibiae. Physical examination of the chest was negative, but the chest roentgenograms of April and July 1951, showed moderate right hilar enlargement. Bronchoscopy had been done previously (April 19, 1951) and was negative. A large left axillary node was found and biopsied, but was reported to be normal. Routine laboratory work was normal except for sedimentation rate of 21 mm. in 45 minutes. The serum albumin was 4.6 grams, and the globulin 3 grams. The blood serology and first-strength PPD were negative.

Re-examination on November 6, 1951 was negative, and the chest roentgenogram showed subsidence of the previously enlarged right hilar shadow.

Case 2: (Mrs. M.J.) This 32-year-old housewife had noted some fatigue and a feeling of weight in the anterior chest since the Fall of 1951, gradually increasing. Swelling of the ankles and tender "red spots on the shins" appeared about February 13, 1952, associated with chills, fever to 101 degrees F., non-productive cough, and a feeling of "tightness" over the precordium. Her physician made the diagnosis of erythema nodosum. Her white count and sedimentation rate were slightly elevated. Physical examination of the chest was negative but the chest roentgenogram showed bilaterally enlarged hilar shadows. She was hospitalized for about 10 days, with gradual subsidence of the skin lesions, though low-grade fever persisted for about two weeks. A roentgenogram of the chest in September 1952, was normal and she was then entirely well.

Case 3: (Mrs. E.D.) This 47-year-old housewife, a deaf mute, developed eye symptoms in September 1949, attributed by an ophthalmologist to a nodular uveitis. In January 1950, she developed the typical skin lesions of erythema nodosum.

associated with slight non-productive cough. The chest roentgenogram of February 27, 1950 demonstrated marked enlargement of the right hilum, and probably an increase in the left hilar shadow as well. Examination in April 1950, showed that red subcutaneous nodules were still present over the left tibia. Fluoroscopy and chest films demonstrated considerable bilateral hilar enlargement.

The diagnosis of sarcoidosis was considered but was not proved, supraclavicular lymph node biopsy and sternal marrow biopsy being negative. A tuberculin test and blood serology were also negative.

First roentgenographic evidence of decrease in the hilar shadows appeared late in September 1950, and the chest x-ray film was not actually considered normal until February 1952. Her uveitis had meanwhile improved, but its presence with the other clinical features is suggestive enough to implicate sarcoidosis as the probable underlying cause.

Case 4: (Mrs. E.H.) This 42-year-old housewife developed erythema nodosum of the lower legs early in March 1950. Low-grade fever and painful tender swelling of the ankles persisted through March. The blood count was within normal limits but the sedimentation rate was 27 mm. in one hour. The chest roentgenogram of March 7, 1950, showed moderate hilar enlargement, more marked on the right. This had increased further in the x-ray film of May 10, 1950, and was associated with moderate widening of the upper mediastinal shadow. Considerable improvement occurred by August 1950, and serial films from December 1950, through December 1952, have been normal.

Discussion

It is probable that the association of hilar lymphadenopathy with erythema nodosum in certain instances represents a distinct entity. In those cases where obvious underlying causes, such as tuberculosis, sarcoidosis, or the acute primary form of coccidioidomycosis seem to have been ruled out, erythema nodosum should be considered as the probable etiological agent. Obviously, appropriate diagnostic studies have to be done in this group of patients. In Case 1, for example, various procedures including lymph node biopsy were done because we thought the patient had either lymphoma or sacroidosis. Sarcoidosis should be thought of in patients with hilar lymphadenopathy and erythema nodosum, but the absence of such findings as an abnormal blood protein picture, roentgenographic changes in the small bones of the hands and feet, and uveoparotid lesions make sarcoidosis less likely.

As previously mentioned, coccidioidomycosis is in a special category because of the endemic nature of the primary form, and the not infrequent association of hilar lymphadenopathy and erythema nodosum. Physicians who do not practice in an endemic area may of course see patients who have recently visited such an area.

The practical significance of the association of hilar adenopathy and erythema nodosum is that persons with these findings may be given a good prognosis, thus sparing them anxiety and often considerable expense. Aside from infectious mononucleosis, primary tuberculosis, sarcoidosis, and coccidioidomycosis, the likelihood of a fatal illness comes to mind when hilar lymphadenopathy, either unilateral or bilateral, is observed. Unfortunately, and all too frequently, a malignant process such as lymphoma, bronchogenic carcinoma, or metastatic malignancy proves to be present.

It is cheering, therefore, to know that hilar lymphadenopathy in the presence of erythema nodosum does not necessarily carry a grim import.

The question arises whether or not deep roentgen therapy is justified in bilateral lymphadenopathy of undetermined cause, if erythema nodosum is present. In our opinion, such patients should be spared the trouble and expense of roentgen therapy, not to mention the worry of an unfavorable prognosis.

SUMMARY

Some of the clinical features and etiological relationships of erythema nodosum have been reviewed, especially the association of hilar lymphadenopathy in a significant proportion of cases. The authors report four cases with this syndrome. When the typical skin lesions are present in a patient with hilar lymphadenopathy, erythema nodosum should be a major consideration in the differential diagnosis of the enlarged hilar shadows.

RESUMEN

Se revisan algunas de las características y las relaciones etiológicas del eritema nudoso, especialmente la asociación con linfadenopatía hiliar en una proporción significativa de casos. Cuando se encuentran las lesiones típicas en la piel en un enfermo con lifadenopatía, el eritema nudoso debe ser un elemento de gran consideración para el diagnóstico diferencial de las sombras hiliares agrandadas.

RESUME

L'auteur passe en revue certains des caractères cliniques de l'érythème noueux et sa signification étiologique. Il montre spécialement la fréquence de l'association avec une atteinte ganglionnaire des hiles. L'auteur rapporte quatre cas caractéristiques de ce syndrome. Quand les lésions cutanées sont constatées chez un malade atteint d'adénopathis hilaire, l'érythème noueux prend une valeur diagnostique considérable pour le diagnostic différentiel des ombres hilaires anormales.

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Resection for Mycotic Pulmonary Disease*

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Reports in the literature and our experience at Kennedy suggest that resection is indicated for some localized mycotic lesions of the lung. It is to this consideration that the following case reports and observation are directed. Systemic mycoses, once considered exotic and obscure diseases, are now recognized to be of such widespread and frequent occurrence that a working knowledge of them is important to every physician. The known incidence of fungus disease in Kennedy patients has tripled since 1949 when two members of our staff became interested in these conditions. Nine cases were recognized in 33,000 patients before 1949 compared to 36 cases in 42,000 patients since 1949, an incidence of almost one in a thousand, which incidentally compares with an incidence of four per thousand for bronchogenic carcinoma.

Recent discovery of the effectiveness of stilbamidine in the treatment of blastomycosis[1,2] has apparently altered the prognosis of this disease. We know of no effective drugs for the treatment of histoplasmosis or coccidioidomycosis of the lung. Large doses of penicillin may be effective against actinomycosis. Stilbamidine has been used successfully also.[3] Dr. Sutliff has used ethyl vanillate with substantial improvement in systemic histoplasmosis but its use has not resulted in improvement in the chronic pulmonary infection.

There are two considerations of prime importance in dealing with pulmonary fungus disease. First, finding the fungi does not rule out the presence of cancer or of tuberculosis. One of our patients with advanced bronchogenic carcinoma was found to have secretions containing many histoplasma capsulatum. Second, the prognosis of persistent mycotic pulmonary lesions is very poor. Dr. Sutliff has found (Table I) that while only 26 cases, or 0.4 per cent of patients had systemic mycoses exclusive of actinomycosis during five years among 6,000 admissions to the Infectious Disease Section, these systemic mycoses accounted for seven (9.2 per cent) of the deaths on this section. This is a mortality of 26.9 per cent for these mycotic lesions. We have come to feel that as a general rule persistent localized pulmonary lesions that do not respond to treatment should be excised. It usually takes three weeks or longer to culture fungi and tubercle bacilli. During this period of time the treatment of a pneumonitis of unknown etiology will probably vary with the history of onset and the location and appearance of the lesion. Pulmonary blastomycosis typically mimics carcinoma; histoplasmosis and coccidiomycosis usually mimic tuberculosis. A chronic pyogenic pneumonitis or the early pneumonitis seen with cancer or due to a foreign body may have the same x-ray appearance and

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clinical picture as these lesions. The pathology found in 437 resected pulmonary lesions is shown in Table II. Effective treatment is dependent upon

TABLE I
KENNEDY INFECTIOUS DISEASE SECTION

	Patients	Deaths
Patients, 1947-1952	6,000	76
Systemic mycosis, excluding actinomycosis	26	7
Incidence of fungus disease	0.4 per cent	
Mortality of fungus disease	26.9 per cent	
Per cent of total mortality	9.2 per cent	

TABLE II
KENNEDY THORACIC SECTION
Pathology of 437 Resected Pulmonary Lesions,
June 15, 1946 to September 1, 1952

Tuberculosis	231	Fungus Disease	6
Malignancy	64	Abscess	32
Bronchiectasis	59	Miscellaneous	45

the work of the pathologist and the bacteriologist who are in turn dependent upon the clinician for selecting and delivering fresh diagnostic material with the request that examination be made for the right organisms and lesions. One usually sees what he looks for and, too often, only what he looks for.

Coccidioidomycosis

Coccidioidomycosis, caused by the organism coccidioides immitis, is a fungus disease endemic to West Texas, New Mexico, Arizona, the San Joaquin Valley and Southern California. It is probably the most infectious of the systemic mycoses, infecting the majority of individuals who live in an endemic area for an appreciable length of time. A comprehensive review of the literature and historical report was made in 1946 by Bass et al.[4] With the increased mobility of the general population and the dissemination of military personnel who have visited or trained in these regions, it is important for all physicians to be cognizant of this clinical entity.

There are several forms the disease may take. The primary and most common is an acute but rather benign, self-limiting respiratory infection. This may rarely lead to the secondary, chronic, granulomatous state in which pulmonary cavitation is often seen. Either may in turn lead to the progressive or disseminated phase which is fatal in more than half of the cases. The primary form, a respiratory infection, is often asymptomatic. The incubation period varies from five to 20 days. When symptoms occur, they resemble those of influenza with sudden onset of chills, fever, chest pain, malaise, productive cough, occasional hemoptysis, joint pain and

sore throat. Occasionally, rash of the erythema nodosum and multiforme types develops between the fifth and the 15th day.[5-7] These symptoms occur in any combination and when mild may be mistaken for the common cold. Many of these lesions, inflammatory in nature, heal leaving no obvious residual pathology. Some progress to the suppurative and granulomatous stage but later heal, leaving residual scars of varying extent.

An occasional infection progresses to chronicity and forms a focal lesion in the form of granulomatou stissue which may or may not excavate. These lesions arouse the most surgical interest because they are amenable to surgical extirpation, represent the form most often seen outside the endemic areas and are often confused clinically with other infectious granulomas or bronchogenic carcinoma. The presence of cavitation considerably complicates the problem, not only in suggesting an alternate and incorrect diagnosis such as tuberculosis and lung abscess per se, but also in causing an added risk to the patient. Greer reported four cases where cavities, usually located peripherally, ruptured causing bronchopleural fistula, coccidioidal empyema and non-expansile lung. The cavities will often close with several months of bedrest but are liable to reopen at any time. Many do not close even after vigorous collapse therapy of various forms.

Dissemination is usually a progression of the initial infection, but may occur from chronic granulomatous and cavernous lesions. Although it may occur late in the disease, the probability of its occurrence and the severity of its course decline with the passage of time from the initial infection.[8] The organism is disseminated via blood and lymph channels. Any body organ may be involved. Dissemination is characterized by marked emaciation, weakness, malaise and fever. Occasionally, subnormal temperature is observed in fulminating cases.

Diagnosis, particularly outside the endemic area, is difficult. Indeed, the pathologist often is the first to make the diagnosis in surgical cases, for in many instances the lesions were resected as tumors of undetermined origin,[8] as tuberculosis or as undiagnosed granulomatous lesions. A high index of suspicion is the first prerequisite aided by a history of exposure, the symptomatology, x-ray examination and the laboratory studies. Physical findings of the chest are variable, inconsistant and usually absent.

The roentgenographic findings have been adequately described by several observers.[9-11] These consist of the following general types:

1) A soft fuzzy hilar infiltration, which may clear in one to two weeks. Seen in approximately 26 per cent.

2) A soft, homogenous, fan-shaped, pneumonitic infiltration extending peripherally from the hilar region. This usually clears in one to two weeks, and is seen in approximately 40 per cent.

3) Pleural effusion, small and transitory, usually an early but not common finding.

4) Mediastinal and hilar adenopathy, seen in about 24 per cent of progressive and chronic lesions.

5) Nodular parenchymal foci, 2 to 3 cm. in diameter, usually single, occasionally multiple. These are the most characteristic findings.

6) Cavitation, cyst-like in appearance, which may or may not resolve spontaneously.

7) Calcification, both peripherally and in the hilar nodes; it is unusual in occurrence.

A positive diagnosis is made when the organism is demonstrated in the smear, culture or animal innoculation. Sputum, pleural fluid, gastric washings and pus from disseminated lesions are examined microscopically.

Surgical extirpation of the localized chronic lesion is the therapeutic method of choice. Desensitization, iodides, colloidal copper, antimony, potassium tartrate, thymol, gentian violet, arsphenamine and the newer antibiotics have been tried without success.

Case 1: S.E.M., a 36-year-old, white male school teacher and farmer was apparently in good health until the summer of 1948 when routine x-ray film examination by a public health mobile unit revealed an infiltrative lesion in the left upper lung field. Sputum examinations at that time were negative for acid-fast bacilli. After a recheck examination one year later, he was told that he probably had an arrested case of tuberculosis. However, re-examination in September 1950 revealed a cavity in the left upper lobe and, consequently, the patient was admitted to the Montgomery, Alabama, Veterans Administration Hospital, October 27, 1950.

At that time he gave a history of productive cough, occasional night sweats and loss of 15 pounds weight during the previous three months. An infiltration in the left upper lobe with a 3.5 cm. cavity underlying the first interspace was found on x-ray examination. Acid-fast bacilli were found in the sputum. Left pneumothorax was instituted November 8, 1950 and pneumonolysis was performed January 19, 1951. Streptomycin, 1 gram daily for 45 days and para-aminosalicylic acid, 12 grams daily for 12 days were given. Another sputum examination in March 1951 revealed acid-fast bacilli.

He was transferred to Kennedy Veterans Administration Hospital on July 27, 1951. On admission, urinalysis was within normal limits; WBC 11,000; 63 neutrophils; 34 lymphocytes; 3 monocytes; RBC 6 million. Repeated sputum examinations were negative for fungi or acid-fast bacilli. Bronchoscopy on August 1, 1951

FIGURE 1 FIGURE 2

Figure 1, Case 1: Admission x-ray film showing infiltration in upper portion of the partially collapsed left lung.—*Figure 2, Case 1:* X-ray film three months postoperatively showing re-expanded left lung with clear lung fields.

revealed a normal bronchial tree with the exception of the left upper lobe bronchus which was displaced inferiorly and laterally.

Chest roentgenogram on admission showed pneumothorax on the left with non-expanding left lung. A dense shadow was present in the upper lobe of the partially collapsed lung (Figure 1).

On August 14, decortication of the left lung, wedge resection of the involved area of the upper lobe, and post-resection, posterior thoracoplasty was accomplished. Postoperative convalescence was uneventful. The patient received streptomycin, 1 gram twice weekly and para-aminosalicylic acid, 12 grams daily for 21 days.

The resected lung tissue, measuring 8 x 5.5 x 3 cm., was more firm than normal and presented a peripheral cavity, 1 cm. in diameter, the wall consisting of a firm white granulation tissue. Microscopically, moderate atelectasis was evident. Alveoli filled with hemosiderin-laden macrophages were noted. The wall of the cavity was lined by a thick layer of chronic granulation tissue containing epitheloid cells, foreign-body giant cells, fibrosis and foci of round cells. The cavity contained caseous debris and areas of granulation tissue undergoing caseous necrosis. Within the resected lung were many discreet lesions characteristic of tuberculosis. Cultures from the tissue grew coccidioides immitis and further study revealed these organisms in the tissue sections of the lesion. Tubercle bacilli were not found in the resected tissue.

A diagnosis of coccidioidomycosis and tuberculosis was made. Postoperative x-ray films showed both lung fields clear (Figure 2) and he was transferred to Montgomery Veterans Administration Hospital on September 12, 1951 for continuance of medical therapy for pulmonary tuberculosis. It is interesting to note that he had not visited any of the known areas endemic for coccidioides. Skin test with coccidioidin was negative. He was examined in September 1952 by Dr. Norman Van Wegel of Foley, Alabama. He was asymptomatic and sputum was negative. A bucky roentgenogram revealed a round area of decreased density opposite the third left transverse process. He reported later that the health department found the sputum positive for acid-fast bacilli in one of two sputum specimens. Re-admission was recommended.

Acceptance of resection for focalized coccidioidomycotic pulmonary lesions is apparently becoming well established. Cotton[12] has reported 30 cases and Melick,[13] in a comprehensive report, collected 109 cases treated by pulmonary resection. The lesion here reported was clinically considered to be tuberculosis on the basis of the positive sputum. The tissue reaction was, as usual in coccidioidomycosis, consistent with that also seen in tuberculous infection. Although the fungus was found in the tissue, these organisms were scattered and not prominent. Had the resected specimen been placed promptly in formalin and immediate cultures not taken, the diagnosis might not have been made, even by the most astute pathologist. The previous reports of acid-fast bacilli in the sputum further complicate the picture, although none were demonstrated from the resected tissue. The coexistence of tuberculosis and coccidioidomycosis is proved by the subsequent positive sputum culture. This incident certainly condemns the casual acceptance of the obvious disease, and shows the pitfalls of the procrustean philosophy of fitting the patient to a single established diagnosis. One of Greer's cases showed pulmonary tuberculosis which became clinically evident three months postoperatively. Of the reported cases, an exceedingly high percentage were resected as unknown types of tumors,

tuberculosis or infectious granulomas, type undetermined. Several reported cases were subjected to resection on the basis of tumor, tuberculosis or other granulomatous infections.

Blastomycosis

North American blastomycosis ("Gilchrist's disease") is a chronic, specific, fungus infection caused by blastomyces dermatitidis. With the exception of a few instances reported from England and Canada, all reported proved cases have occurred within the United States, predominantly in the Mississippi River Valley area.

Two clinical forms are recognized, cutaneous and systemic. The cutaneous form, typically, is manifested by a solitary chronic or subacute ulcerating lesion; secondary systemic involvement is rare. However, systemic blastomycosis frequently involves the skin secondarily and often the patient has widespread involvement of many internal organs. The lung is a focus in approximately 96 per cent of the cases, and the spleen, liver, bones, prostate and central nervous system may show involvement. Most cases of systemic blastomycosis begin with pulmonary infection.[14] This phase of the disease is nearly always fatal. Martin[16] and Smith note a mortality of about 92 per cent.

The onset of pulmonary infection is characterized by insidious, but progressive, symptoms such as may be found in any ordinary, subacute, respiratory infection. Low-grade fever, pleuritic-type chest pain, dry cough, malaise, weakness and dyspnea may be seen. Purulent sputum, with or without mild hemoptysis, develops within a month or two as the infection progresses. In this later state the initial weakness, dyspnea and fever increase in severity and night sweats are of frequent occurrence. The patient shows loss of weight, appears chronically ill, and may show evidence of dissemination of the disease.

Roentgenographic examination of the lungs may show several changes. Most frequently, hilar and mediastinal adenopathy is seen. While this is often present without evident parenchymal involvement, in many cases there is an associated, irregular, dense shadow extending peripherally from the hilus. This latter finding is so suggestive of carcinoma that frequently the lesion is removed with that diagnosis in mind. Cavities are unusual and when present are small, irregular and thin walled. A scattering of miliary lesions may be seen.

It is necessary to resort to laboratory tests to make an unequivocal diagnosis. The organism can be identified in a direct smear from an available lesion or from sputum.

Baker[15] expressed the belief that microscopic sections showing the characteristic tissue reaction are sufficient for absolute diagnosis. He has described in detail the histopathologic observations characterizing blastomycotic infection. These lesions are essentially the same regardless of the organ in which they occur. The typical lesion consists of inflammatory granulomatous tissue containing blastomycetes, polymorphonuclear granulocytes, plasma cells, epithelioid cells, foreign-body giant cells and necrotic

debris. The presence of miliary abscesses and the predominance of polymorphonuclear neutrophils within these abscesses help to differentiate blastomycosis from tuberculosis, even in the absence of demonstrable specific organisms. In routine sections stained with hematoxylin and eosin, the organism is seen as a rounded structure with thick double-contoured walls.

Dr. W. D. Sutliff considers therapy with stilbamidine preferable to any other at this time. Others think it may be specific therapy for the disease. Improvement was seen in all five cases treated by Dr. Sutliff on the infectious disease section at Kennedy. Three cases, one with a cutaneous lesion and two with visceral involvement, were discharged from the hospital with no evidence of active disease. Certain cases, as yet not clearly defined, may need resection while receiving stilbamidine, in the manner that tuberculosis is now treated with antibiotics and resection of the nonhealing caseous or cavitary areas.

Case 2: (Previously reported.[27]) A colored male, 30 years of age, was admitted to Kennedy Veterans Administration Hospital on April 19, 1949 complaining of weakness, anorexia and malaise of one month's duration. A few days after onset of these symptoms, the patient experienced chills, fever, night sweats and left chest pain, all of which occurred intermittently for two weeks. Four days previous to admission, hemoptysis of approximately one ounce of bright red blood occurred. On admission physical findings were within normal limits with the exception of diminished breath sounds and slightly impaired percussion note over the right lower chest posteriorly. Roentgenograms revealed a circumscribed homogeneous density in the right lower posterior lung field, adjacent to the cardiophrenic angle (Figure 3). Laboratory studies were all within normal limits with the exception of a sedimentation rate of 32 mm. per hour, corrected. Sputum smears and cultures for acid-fast bacilli and fungi were negative. Bronchoscopic examinations were non-contributory.

A therapeutic and diagnostic trial of penicillin, 200,000 units every three hours, for 15 days failed to alter the roentgenographic appearance of the lesions. On May

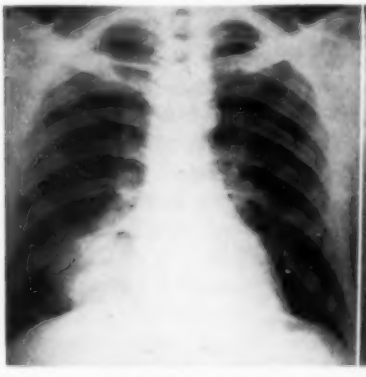

FIGURE 3

FIGURE 4

Figure 3, Case 2: Roentgenograph on admission showing lesion in the right lower posterior lung field adjacent to the cardiophrenic angle.—*Figure 4, Case 2:* Seven months postoperatively.

23, 1949 posterolateral thoracotomy was done through the site of the resected right seventh rib. A firm, irregular mass, 8 cm. in diameter, was found in the lower lobe and removed by lobectomy. Frozen sections were reported as granulomatous lesion, type undetermined. A hilar lymph node dissection was done.

Examination of the resected tissue revealed, grossly, a rounded, firm mass, 8 cm. in diameter, in the posterior portion of the lobe. This lesion had a variegated, yellowish hue and blended into the surrounding normal lung tissue, no capsule being evident. On microscopic examination, a granulomatous, fibrous stroma was seen in which miliary abscesses surrounded by epithelioid cells, foreign-body giant cells, chronic inflammatory cells and the organisms of blastomycosis were found. Many of these organisms showed typical buds. Acid-fast and aniline blue stains of tissue sections revealed no other pathogens. Cultures confirmed the presence of blastomyces dermatitidis.

The postoperative course was uneventful (Figure 4) and he remained symptom-free when last located in September 1951.

Case 3: L.E.P., a white male, 40 years of age, was admitted to Kennedy Veterans Administration Hospital on June 29, 1951. In 1949 he had been previously hospitalized elsewhere for three months where on the basis of loss of weight, dyspnea and chest pain a tentative diagnosis of pulmonary tuberculosis was made but no tubercle bacilli were found. With the exception of mild weight loss he remained relatively symptom-free until one month previous to this admission when he noted a minimal cough productive of mucopurulent sputum with occasional blood streaking. Physical examination on admission was within normal limits.

Laboratory examination showed WBC of 10,650, normal differential with the exception of 8 per cent eosinophils. Repeat white count showed 2 to 5 per cent eosinophilia. Blood sugar was 398 mg. per cent on admission. While on the pulmonary disease section of Dr. Sam Phillips, the sputum smears and cultures were negative for acid-fast bacilli but the organism blastomyces dermatitidis was repeatedly found. Roentgenographs revealed a mottled infiltration involving the upper one-third of the left lung with numerous small radiolucencies within the area of infiltration (Figure 5).

The diabetes was readily controlled with 35 units of NPH insulin and a diabetic diet. Skin tests with blastomycin, coccidioidin and histoplasmin were negative. On August 9, 1951 potassium iodide, 5 minims three times a day, was given and

FIGURE 5 FIGURE 6

Figure 5, Case 3: Preoperative x-ray film showing lesion of left upper lobe.
Figure 6, Case 3: Three months postoperatively showing clear lung fields.

daily increased 1 minim each dose until 27 minims three times a day were given and this dosage was continued throughout the hospital stay.

On August 28, 1951 left upper lobectomy with resection of a small portion of the superior segment of the left lower lobe was done. Findings at surgery were scattered nodules within, and confined to, the resected lung tissue. A partial posterior thoracoplasty was accomplished at the same time.

Examination of the resected tissue revealed, grossly, a diffuse spread within the lung tissue of small, light colored nodules, 1 to 4 mm. in diameter. Microscopically, areas of caseous necrosis surrounded by granulation tissue, fibrosis, chronic inflammatory cells and typical organisms of blastomycosis were seen. Cultures proved the organism to be blastomyces dermatitidis.

The postoperative course was uneventful with the exception of minimal pleural effusion on the left side. He left the hospital against medical advice on November 22, 1951 at which time the lung fields were clear on x-ray film examination (Figure 6). He returned for examination on October 10, 1952. Roentgenogram of the chest showed no change. Cultures of the sputum were negative November 1, 1952. He is now convalescing from gastric resection for an obstructing benign gastric ulcer.

The first case of blastomycosis was thought preoperatively to represent carcinoma of the lung. Cultures were not obtained of the resected lesion, but the histological picture was typical. This case was partially responsible of rthe decision at this clinic to culture immediately all surgically removed pulmonary lesions. The value of this policy is apparent in the other cases reported here. The second case was diagnosed correctly preoperatively from sputum examination and proved by cultures as well as by histology. A similar case was encountered where right upper lobectomy, ostensibly for tuberculosis, was done. Histology was similar to the two cases here reported, but the organisms were few in number, did not show budding and cultures were negative for fungi and acid-fast bacteria. The diagnosis must remain in doubt, as it also must in other non-specific granulomas we have encountered. Perhaps better methods of study will, in the future, allow us to make a specific identification of many such lesions.

Incision and drainage for some deep-seated foci and debridement of cutaneous blastomycotic involvement have long been advocated. It is surprising, therefore, that we could find no advocacy for resection of pulmonary lesions, nor did our review of the literature reveal any incidence of resection of pulmonary blastomycosis with apparent cure. Smith[14] reports three cases of blastomycosis incorrectly diagnosed as carcinoma of the bronchus, in one of which lobectomy was performed. No information is given as to the subsequent clinical course of this patient. One case of resection of a blastomycotic lesion has been recently reported from the Mayo Clinic.[17]

Histoplasmosis

Histoplasmosis is a specific fungus infection caused by the organism histoplasma capsulatum. This organism differs from the other pathogenic fungi in attacking primarily the reticulo-endothelial system. The disease has been reported from North, Central and South America, the Philippines, Java, South Africa and England.

There is much uncertainty and question related to the clinical types

and incidence of the disease. Particularly in doubt is the role this disease plays in pulmonary calcification. It was previously considered a rare and invariably fatal illness until studies by Christie[18] in Tennessee and Palmer[19] in Kansas, Missouri and Ohio indicated the presence of a benign type which is widespread, at least in the Mississippi Valley. These studies were predicated upon the specific skin test with histoplasmin. This form appears to give rise to small calcified lesions in the periphery of the lung associated with calcification in the hilar lymph nodes. The patients, demonstrating positive skin tests to histoplasmin, do not usually have a significant history of previous clinical pulmonary infection. This phase of the disease appears to be analogous to the benign form of coccidioidomycosis.

The disease, as usually described, differs widely from the benign and asymptomatic type and may be termed the progressive, disseminated phase; it is usually fatal. Most of the reported cases have been diagnosed only after necropsy. The organism is thought to enter the body through the gastrointestinal tract. Oral, pharyngeal and laryngeal lesions are frequently seen, as are intestinal ulcerations and mesenteric adenopathy.[9] Only occasionally are the lungs the primary site of involvement, although pulmonary involvement is not uncommon and may be the outstanding clinical lesion or even the sole lesion. The lungs are almost always involved in generalized disseminated cases. There is no apparent explanation why more progressive severe pulmonary disease is not seen when the benign primary pulmonary form is so prevalent and widespread. Perhaps the infection is analogous to tuberculosis where an allergic response differentiates the "childhood" primary disease from the more malignant, reinfective phase.

Symptomatology is not specific; Darling[21] originally enumerated fever, emaciation, anemia and splenomegaly as the prominent findings. Lymphadenopathy, hepatomegaly, purpura, relative lymphocytosis, diarrhea, rales in the chest, chronic cough and oral nasopharyngeal ulcerations are occasionally noted.[9,22,23]

The specific diagnosis must be made by the medical laboratory. History alone may only suggest the diagnosis while physical signs are equivocal and minimal. Chest findings are usually limited to rales. The usual picture on x-ray film examination of the chest is that of non-specific hilar adenopathy, scattered nodules or a parenchymal infiltration usually with cavitation. Smears from accessible ulcerative lesions, thick and thin preparations of peripheral blood and sternal marrow smears are stained with Wright's or Giemsa's stain. The organism, a small oval body 1 to 5 microns in diameter, is found in the large mononuclear cells. Budding may be noted. Tissue sections may show caseous and liquefaction necrosis, tubercle formation or a diffuse involvement of the reticuloendothelial elements. The phagocytes and macrophages contain large numbers of the organisms which may be seen in hematoxylin and eosin preparations but which are more prominent with Gram's stain.

In general the treatment has been unsatisfactory. Metals, iodides, roentgen therapy and antibiotics have all been tried and proved ineffectual.

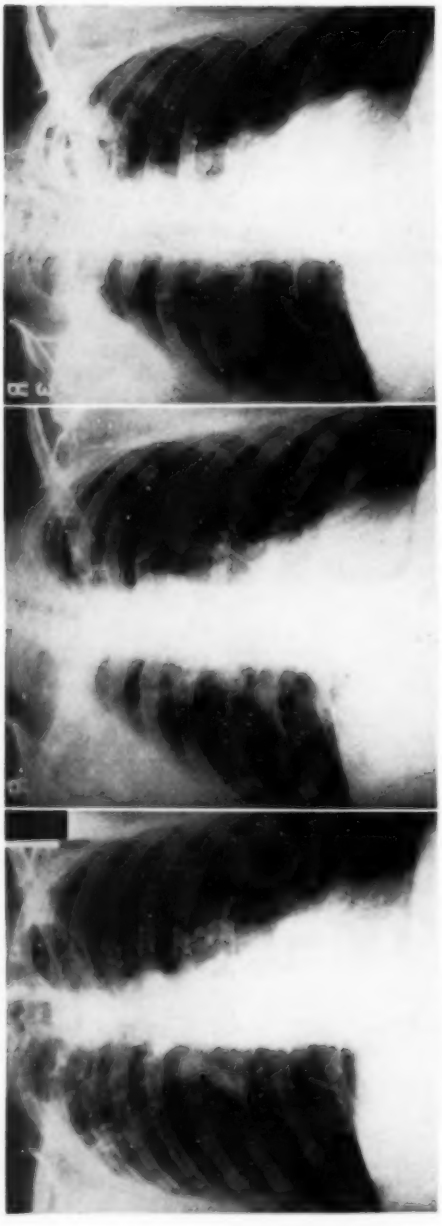

FIGURE 7 FIGURE 8 FIGURE 9

Figure 7, Case 4: Admission x-ray film showing right upper lobe infiltration.
Figure 8, Case 4: Two months postoperatively.
Figure 9, Case 4: Four months postoperatively. Tuberculous involvement of the left upper lobe is evident.

The chronic pulmonary lesions have not responded to ethyl vanillate in Dr. Sutliff's experience.

Case 4: C.W., a white male, 43 years of age who, on the basis of x-ray film findings at the Arkansas State Sanatorium in October 1948, was diagnosed as having pulmonary tuberculosis. At that time one gastric washing had been positive for acid-fast bacilli but none had been found subsequently. He was discharged June 1949 but readmitted October 1949 because of an infiltration in the right lung which was thought to represent a spread of tuberculosis. In November 1950 right phrenemphraxis was done following an unsuccessful attempt to produce therapeutic pneumothorax. No antibiotics had been given.

Hemoptysis occurred in August 1949 associated with a three-day elevation of temperature to 100 degrees. He developed cough productive of blood-streaked sputum. He was seen at another Veterans Administration facility where acid-fast bacilli could not be demonstrated but where he responded so well to penicillin and terramycin that a diagnosis of bronchiectasis was entertained in addition to that of tuberculosis and he was transferred to Kennedy Veterans Administration Hospital on June 6, 1951 for further study and therapy.

On admission the physical examination was within normal limits with the exception of decreased respiratory excursion of the right side of the chest.

Laboratory examination showed WBC of 4,200; 46 per cent neutrophils; 44 per cent lymphocytes; 9 per cent eosinophils and 1 per cent monocytes. Red blood cells 5.05 million. Sedimentation rate 35 mm. per hour, corrected. Sputum examination, bronchial secretions and gastric washings were negative for acid-fast bacilli and fungi. Roentgenograms revealed a mottled and linear infiltration of the upper one-half of the right lung field. Within the infiltration several small radiolucencies were noticed (Figure 7). Bronchoscopy was non-contributory. Bronchograms showed incomplete visualization of the right upper lobe.

It was felt that this pathology represented tuberculosis and that bronchiectasis did not exist. He was started on streptomycin, 1 gram twice weekly with 12 grams of para-aminosalicylic acid every day with the intention of keeping his tuberculosis under control. Right upper lobectomy on August 3, 1951 was followed by empyema in the right upper pleural cavity that responded to closed drainage and posterior apical thoracoplasty (Figure 8).

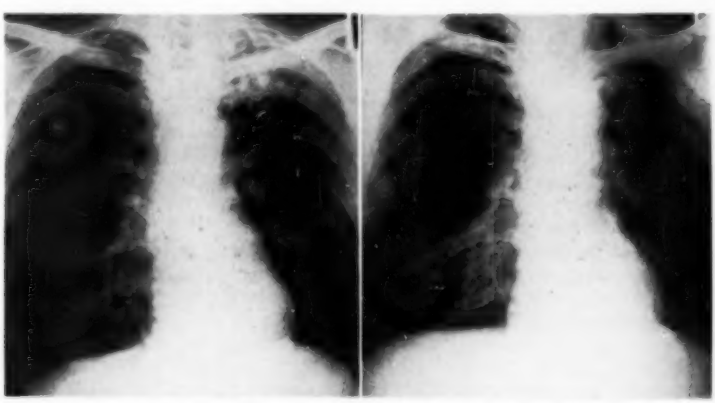

FIGURE 10 FIGURE 11

Figure 10, Case 5: Preoperative x-ray film showing infiltration in the left upper lobe.
Figure 11, Case 5: Final results. No evidence of residual disease.

The resected specimen consisted of a lobe of lung tissue which measured 14 x 11 x 6 cm. The bronchi were opened and two branches, near the base of the lobe, lead into a cystic cavity which was empty. The wall consisted of a reddish, granular, friable, granulation tissue covered by greyish exudate. The surrounding parenchyma contained numerous, small, discreet, firm nodules, greyish white on cut surface. Microscopically, the cavity was lined by necrotic debris beneath which chronic inflammatory granulation tissue with a diffuse and peribronchial infiltration of round cells was seen. Numerous scattered tubercles were present with caseous centers and a surrounding zone of cellular fibrosis and chronic inflammatory cell infiltration. A few foreign-body type giant cells were present. The surrounding lung parenchyma revealed numerous epithelioid cells, foreign-body giant cells and macrophages, the latter containing many small bodies consistent in appearance with the organism of histoplasmosis. Cultures showed these to be histoplasma capsulatum.

On September 13, 1951 there appeared an infiltration in the left apex (Figure 9). He was transferred to the infectious disease section where Dr. Sutliff on October 29, 1951 began ethyl vanillate therapy in increasing doses until 48 grams a day was reached and this was continued until November 22, 1951. A therapeutic level of 21 to 23 mg. per cent was maintained. On October 20, 1951 he had hemoptysis and sputum cultures were reported positive for acid-fast bacilli on November 22. Consequently, it was felt that the pathology in the left apex represented tuberculosis rather than an additional focus of histoplasmosis, and therapy with streptomycin and PAS was begun. At the present time he is remaining on the above therapy for tuberculosis.

Case 5: E.B., a white male, 54 years of age, was first admitted to Kennedy Veterans Administration Hospital on April 12, 1950 for vague postprandial pain occurring intermittently for 20 years. Gastrointestinal study failed to show any disease, but an incidental finding of a band-like infiltration in the upper lobe of the left lung was made. Repeated sputum smears and cultures for acid-fast bacilli and fungi were all negative. Bronchoscopic examination was non-contributory. A diagnosis of pulmonary fibrosis, etiology undetermined, was made and he was discharged on May 18, 1950 but returned on March 28, 1951 complaining of left chest pain, cough, frequent colds and loss of weight. Physical examination on this admission was completely normal, except for scattered inspiratory dry rhonchi in the region of the scapula. No posttussive rales were noted.

Laboratory examination showed RBC 4.9 million; 77 per cent neutrophils; 19 per cent lymphocytes; 4 per cent monocytes. WBC 6,900; sedimentation rate 2 mm. corrected, sputum and gastric washings negative for acid-fast bacilli and fungi. Roentgenographic studies showed the infiltration previously mentioned, with some extension and cavitation (Figure 10). Bronchoscopy was again non-contributory.

On May 21, 1951 the posterior apical segment of the left upper lobe, along with wedge-shaped portions of the tip of the superior segment and anterior segment were removed. On June 22, 1951 post-resection thoracoplasty was accomplished. Postoperative convalescence was uneventful.

The specimen consisted of resected pulmonary tissue, measuring 13 x 8 x 5 cm., which contained a 3 cm. cavity peripherally. The cavity was surrounded by indurated tissue. Microscopically, the cavity was seen to be filled with necrotic debris, and about the periphery of the cavity and throughout the parenchyma, there were areas of granulation reaction, showing epithelioid cells, chronic inflammatory cells and an occasional foreign body giant cell. Areas of central necrosis were present within several granulomatous nodules. Cultures revealed histoplasma capsulatum. No acid-fast bacilli could be found on smear, culture or section. A diagnosis of histoplasmosis was made.

The patient did well postoperatively and was retained in the hospital for convalescence and study for further disease. When discharged in December 1951 and

examined in March and September 1952, there was no evidence of pulmonary histoplasmosis (Figure 11).

The first case, initially diagnosed tuberculosis, either had coexistent disease or developed tuberculosis secondarily. Also of interest is the apparent recession of the disease with penicillin and terramycin. Acid-fast bacilli were not demonstrated in the resected tissue. The subsequent tuberculosis is well established however. Coexistent tuberculosis and histoplasmosis are not unusual; it is mentioned by Conant. Meloney found H. capsulatum as a concomitant or secondary infection in two cases of pulmonary tuberculosis. The second case, resected as an undiagnosed lesion, has not had sufficient time postoperatively to be considered an apparent cure although at this time he shows no evidence of the disease. Cavitation was present in both cases. Neither showed the scattered calcification indicative of an earlier primary benign histoplasmosis infection. In a search of the literature only three previous cases of resection for histoplasmosis could be found. Two of these showed marked benefit.[24]

Discussion

It seems evident that although resection of pulmonary fungus infections is not a new concept, with the exception of coccidioidal disease it has not been generally advocated. Resection has been previously employed for other non-fungoid lesions. In our limited experience, it has appeared to offer progress toward an effective form of therapy in a field where therapeutic methods are scarce and unreliable. Our experience confirms the concept, which is becoming increasingly prevalent, that if feasible an undiagnosed, circumscribed or localized, pulmonary lesion should be excised. Procrastination and delay of many months for diagnosis by a lengthy, involved process of elimination may carry more danger than early operation.

In most cases a period of six to eight weeks should be sufficient to establish the diagnosis, to start specific therapy, if any is available, and to

TABLE III
KENNEDY THORACIC SECTION
June 15, 1946 to September 1, 1952
Operative mortality (60 day)

Operation	Number	Deaths	Per cent
All major operations	1530	22	1.4
All pulmonary resections	437	8	1.8
Resection for malignant lesions	64	5	7.7
Resection for benign lesions	373	3	0.8
Pneumonectomy for malignant L.	37	2	5.4
Pneumonectomy for benign L.	33	3	9.1
Subtotal resection, benign L. VA	340	0	0.0
Subtotal, benign L. Army and VA	576	1	0.17

establish the clinical and roentgenographic course of the disease. The result of the administration of the specific therapeutic agent would then determine the necessity for surgery.

The high mortality of systemic fungus infection is well known and the experience at Kennedy is shown in Table I. The 26.9 per cent mortality of systemic fungus disease does not compare favorably with the present low mortality of pulmonary resection as shown in Table III. Any localized pulmonary lesion may give rise to a systemic lesion at any time. It can be noted that the overall operative mortality, or deaths in the 60 days immediately postoperative, of the 1,530 major thoracic operations performed between June 15, 1946 and September 1, 1952 was 1.4 per cent. Further, 340 resections of a portion of the lung for a benign lesion were not followed by an operative death and if our Army series of 236 lobectomies with one death is added we have a series of 576 subtotal resections with one operative death. A greater mortality is expected if a complete lung must be removed or if a malignant disease is present. The mortality in these cases is most often the mortality of the lesion present and not attributable to the surgery, per se.

Although the risk of surgery of the lung is relatively small, it still remains to be proved that resection will aid in the complete cure of fungus infection. We know that many cases will be improved by surgery and that the disease is temporarily alleviated. We believe that, at the present time, resection of localized chronic pulmonary lesions due to coccidioidin immitis or to histoplasma capsulatum is indicated. The administration of stilbamidine is indicated for blastomycosis of the lung. If there are residual lesions that do not clear after adequate therapy resection is indicated.

All too often, sputum examinations are ordered and collected in a routine and inadequate way. Kurung[25] describes in detail methods and procedures which are valuable in obtaining better results. At Kennedy cultures of resected tissue are taken in the operating room immediately after excision. At this time, the specimen is dissected and the lesion inspected. If indicated, frozen sections are obtained. When taking cultures, it is well to include a portion of tissue to insure an adequate sample in a fresh, moist state.

The coexistence of tuberculosis and mycotic pulmonary infections is noted in several previously reported cases[26] and in two instances here. At this time both cases show evidence of tuberculosis. It is logical to assume that a person, weakened by a chronic, debilitating disease, who carried within his pulmonary tissue a locus minoris resistentiae, would be exceedingly susceptible to a superadded pulmonary infection. Whether the initial infection were tuberculosis or mycosis would be difficult to determine.

SUMMARY

1) The pulmonary lesions of coccidioidomycosis, blastomycosis and histoplasmosis are discussed as to occurrence, symptoms, laboratory findings and pathology.

2) Three cases where pulmonary mycotic lesions were resected with

clinical improvement and possible cure are presented in detail. Two cases of tuberculosis and mycosis continue to have tuberculosis.

3) The problems of the diagnosis and management of pulmonary mycotic infections are discussed.

4) The similarities and frequent coexistence of pulmonary tuberculosis and mycotic infections are noted.

5) Resection is probably the therapy of choice in selected, chronic, localized, pulmonary, fungus infections that remain after specific therapy or for which there is no effective therapy.

RESUMEN

1) Se discuten en lo referente a su ocurrencia, sus síntomas, hallazgos de laboratorio y anatomía patológica, las lesiones pulmonares de la coccidioidomicosis, blastomicosis e histoplasmosis.

2) Se presentan en detalle tres casos en los que las lesiones pulmonares micósicas fueron resecadas con mejoría clínica y posible curación.

3) Se discuten los problemas del diagnóstico y el tratamiento de las infecciones pulmonares micósicas.

4) Se hacen notar las similaridades y la frecuente coexistencia de las infecciones pulmonares micósicas y tuberculosas.

5) La resección pulmonar es probablemente el tratamiento de elección en las infecciones fungosas crónicas, localizadas bien seleccionadas en el pulmón, que restan después de la terapia específica o para aquellas que no tienen un tratamiento efectivo.

RESUME

1) Les auteurs discutent, à propos des lésions pulmonaires de coccidiodomycose, de blastomycose et d'histoplasmose, leur fréquence, leurs symptômes, les constatations biologiques et anatomo-pathologiques.

2) Ils présentent en détails trois cas chez lesquels, à la suite de l'exérèse des lésions pulmonaires mycotiques, on constata une amélioration clinique et même une possibilité de guérison. Chez deux malades où existaient simultanément une tuberculose et une mycose, la tuberculose continua à évoluer.

3) Les auteurs discutent le problème du diagnostic et du traitement des infections pulmonaires mycotiques.

4) Ils notent l'analogie et la coexistence fréquente de la tuberculose pulmonaire et des infections mycotiques.

5) La résection est probablement la thérapeutique de choix pour certaines lésions fongiques, chroniques, localisées, qu'elles soient le reliquat d'un traitement spécifique ou qu'elles n'aient pas pu être influencées par la thérapeutique.

References will appear in reprints.

Pulmonary Insufficiency and Death Following Pneumoperitoneum and Phrenic Crush for Pulmonary Tuberculosis. Case Report

PINHAS WAYL, M.D., F.C.C.P. and LEON E. FARHI, M.D.
Jerusalem, Israel

There have been few reported cases of untoward effects following pneumoperitoneum and in most cases these have regressed after treatment was discontinued. The case here reported is one of pulmonary insufficiency and death following pneumoperitoneum and phrenic crush.

Case Report: A 33 year old woman began to complain of productive cough, fatigue and fever in April 1948. In May a tuberculous cavity was found in the upper lobe of the right lung (Figure 1) and in June pneumothorax was induced. In October, thoracoscopy and cauterization of adhesions were performed. In July 1949, a cavity appeared in the left middle lung field (Figure 2). An attempt to induce pneumothorax on this side was unsuccessful. She was discharged one month later, although tubercle bacilli were still present in sputum smears.

In January 1951, refills of the right pneumothorax were discontinued. While the air was being resorbed a small amount of fluid accumulated, which persisted until all the air had disappeared. During this process, the mediastinum shifted to the right. A round infiltrate was then found in the region of the cavity in the left middle lung field (Figure 3). In February she complained of increased cough and expectoration. A chest x-ray film showed that the round infiltrate had been replaced by a cavity, measuring 3 x 5 cms. (Figure 4). In March the patient was referred to this hospital.

On admission, she was approximately 15 Kg. overweight, and had no dyspnoea or cyanosis. There were signs of pachypleuritis on the right side and rales at the left basis. Red blood cell count was 4,240,000 with 12.5 Gm. hemoglobin. Vital capacity was only 1,100 cc. but the patient did not appear to be cooperating fully. Numerous tubercle bacilli were found in the sputum.

Laminography showed a cavity in the apical segment of the left lower lobe (4 to 5 cm. from the dorsal surface of the chest) (Figure 5). The right pleura was thickened, especially over the apex, which was occupied by several linear and round shadows suggesting cavitation. The trachea was shifted to the right.

Since we have had very good results with pneumoperitoneum treatment of cavities in the apex of the lower lobe,[1] and since no choice was left to us, pneumoperitoneum was induced and after three months, there was definite radiological evidence of improvement in the left lung, and the size of the cavity was reduced to 2 x 3.5 cms. (Figure 6). Vital capacity fell to 900 cc. There was a 4 Kg. weight loss. In order to increase the degree of the collapse, left phrenic crush was done on August 5, and no immediate after-effect was noticed. After one month, shortness of breath on moderate exercise gradually developed. Serial chest x-ray films showed further shrinkage of the cavity (Figure 7), and its replacement by an homogeneous fibrous shadow in November (Figure 8). At this time the sputum was negative for tubercle bacilli (for the first time since onset of the illness in 1948). Red blood cell count was 4,560,000 with 14 Gm. hemoglobin on November 4. Pneumoperitoneum refills were continued during this period, giving a final pressure reading of around 15 cm. of water after 1,000 cc.

In September, she started complaining of nausea and vomiting, which responded to atropin. During November regularly recurrent headaches developed. Neurological examination was negative. Venous congestion of the retina was reported on December 17, but not subsequently. The cerebrospinal fluid showed no ab-

normal findings, except for a slight elevated sodium chloride level of 770 mg. The electrocardiogram showed only slight change, possibly due to the transverse position of the heart. Headache was progressively more intense, until it became permanent. In December, following discovery of cyanosis of the nail-beds, refills of pneumoperitoneum were discontinued. Since cyanosis increased, 1,000 cc. of air were withdrawn from the peritoneal cavity, but no improvement of cyanosis or headache occurred. Tachypnoea and tachycardia soon became part of the picture. On January 7, 1952, moist rales were heard on both sides of the chest. Examination of arterial blood showed an oxygen saturation of 72 per cent, and an hematocrit of 60 per cent. Red blood cell count had risen to 5,870,000 with 15 Gm. hemoglobin. Air was withdrawn again from the peritoneal cavity. Since the increase in hematocrit doubtlessly caused and added burden to the heart, it was decided to perform phlebotomy and administer intravenous digitalis and strophantin. The patient did not respond to treatment and died on January 12. Permission for post-mortem examination was not granted.

Discussion

The pulmonary insufficiency in this case can be attributed to a number of causes, which we shall analyze briefly.

It is possible that pneumoperitoneum and phrenic crush caused such a marked degree of lung collapse that ventilation was impeded. Nevertheless, our experience with this treatment includes several cases where the collapse was as great as in the present case, yet the patients were able to carry on their usual activities. Besides, the changes proved to be irreversible after air was withdrawn from the pneumoperitoneum and ventilatory capacity was increased.

Numerous authors have stressed the harmful effects of pneumothorax on the lung, as seen in clinical,[2] functional,[3] and angiocardiographic[4,5] studies. Angiocardiography also shows decreased vascularity in lungs sub-

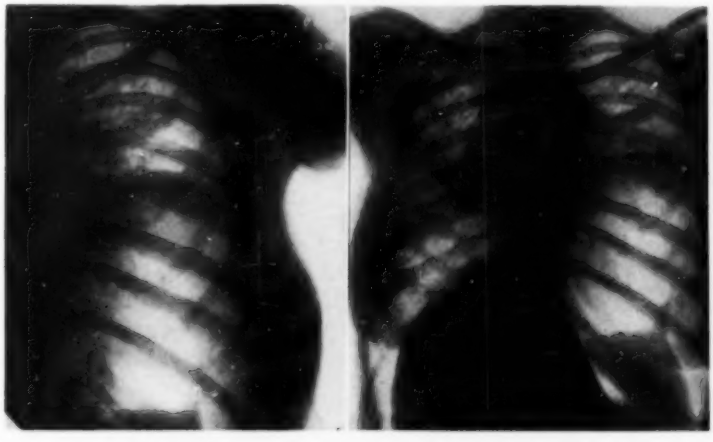

FIGURE 7 FIGURE 8

Figure 7: X-ray film taken September 20, 1951. Six weeks after phrenic crush on the left side. Fibrosis has taken place and the cavity is almost completely obliterated.—*Figure 8:* X-ray film taken in November 1951. The cavity has now completely disappeared.

FIGURE 1 FIGURE 2 FIGURE 3

Figure 1: X-ray film taken June 7, 1948. Small cavity surrounded by infiltration just below right clavicle.—*Figure 2:* X-ray film taken July 12, 1949. Extensive pneumothorax on the right side and new cavity at level of the left 7th rib posteriorly. *Figure 3:* X-ray film taken November 11, 1950. Shift of mediastinum to the right and infiltration replacing cavity on left.

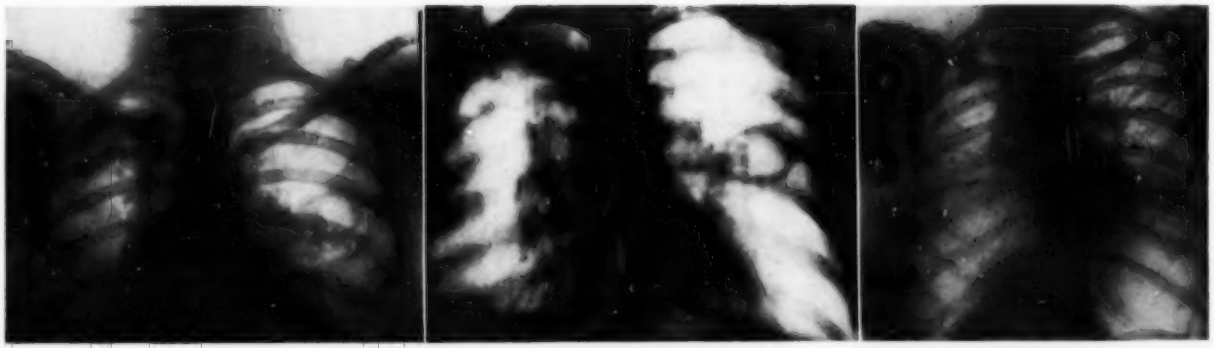

FIGURE 4 FIGURE 5 FIGURE 6

Figure 4: X-ray film taken March 14, 1951. Right hydropneumothorax still present. Mediastinal shift accentuated. In the left infiltrate, cavitation has taken place.—*Figure 5:* Laminograph, taken March 28, 1951. Distance from back: 5 cms. Extreme tracheal deviation to the right. The right apex reaches only up to the third rib posteriorly. Opaque shadow above it. Cavitation present in the apex. Huge cavity in left middle lung field. — *Figure 6:* X-ray film taken July 7, 1951. Three months after induction of pneumoperitoneum. Further reexpansion of the right lung, and shrinkage and flattening of the cavity on the left.

jected to pneumoperitoneum.[6] In some reports it is pointed out that the healthy lung tissue compensates by an increased blood flow, when circulation is diminished in the rest.[7] As seen in Figure 2, the collapse of the right lung under pneumothorax was severe and it is quite probable that the greatest part of the pulmonary circulation was diverted to the left. Subsequent collapse of the left lung started a vascular fibrosis which resulted in reduced oxygen transfer.

The theory that death was due to oxygenation deficiency and not to ventilatory insufficiency readily explains the insidious irreversible course in this case.

Our conclusion is that pneumoperitoneum in conjunction with phrenic crush is far from being an innocuous procedure and may give rise to serious complications. This is particularly true when extensive contralateral collapse has previously been present.

SUMMARY

A case is presented in which treatment by pneumoperitoneum and left phrenic crush after termination of right pneumothorax was followed by pulmonary insufficiency and death. It is suggested that pneumoperitoneum in conjunction with phrenic crush may be dangerous when functional impairment of the contralateral lung is suspected.

RESUMEN

Se presenta un caso en el que el tratamiento con neumoperitoneo y frenopraxis izquierda después de terminar un neumotorax derecho fué seguido de insuficiencia pulmonar y muerte. Se sugiere que el neumoperitoneo en conjunción con la frenopraxis puede ser peligroso cuando se sospecha que hay incompetencia funcional del pulmón contralateral.

RESUME

Les auteurs présentent une observation d'un malade qui était porteur d'un pneumothorax droit, et chez qui, après cessation de ce pneumothorax, un écrasement du phrénique gauche et un pneumopéritoine furent suivis d'une insuffisance pulmonaire mortelle. Ils pensent qu'un pneumopéritoine, associé à une paralysié du nerf phrénique peut être dangereuse lorsque la capacité fonctionnelle du poumon opposé semble insuffisante.

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Medical Student Teaching at Trudeau Sanatorium*

GORDON M. MEADE, M.D., F.C.C.P.**
Trudeau, New York

Instruction of medical students in tuberculosis and the fundamentals of chest diseases in general has been part of the program of Trudeau Sanatorium for many decades. It has three approaches.

First, instruction of those medical students who have come to the sanatorium as patients. This, of course, has been a fortuitous approach but nevertheless over the past 40 years has resulted in generating a spark which in many instances has led to a life long interest or even specialization in chest disease. With such students the element of fear of infection has not been present and hence was no problem. They have been allowed to participate, as their activity allotment increased, in staff rounds, weekly staff conferences, work-up of new cases and progress reports, x-ray readings and laboratory work. This approach to tuberculosis teaching, of course, is not of any consideration as a calculated one and is mentioned largely because of historical and background interest. In working with these student patients, we gradually evolved our methods used with the other students.

Second, for about 35 years we have offered externships for eight weeks during July and August to medical students who have completed their third year. Four to six students have been received each summer from a considerable number of the country's medical schools. Students of one year have tended to recruit students from their schools for the succeeding summer. In certain schools it has become a tradition for some of the students to spend the summer at Trudeau. In addition to self recruitment, in the past five or six years we have sent a notice of the externships to the deans of a number of medical schools.

There has been a steady narrowing of the sources from which such students can come as an increasing number of schools have made the fourth year an all year course by eliminating the summer recess after the third year. But a sufficient number of schools still retain the recess period so as to afford us no real difficulty in securing our quota of students. In fact, often we cannot accept all who apply.

These students are supplied with room and board from funds available to us for teaching purposes. We have always carefully preserved an atmosphere of contribution by us to the student rather than the reverse. Students are not asked to do "scut" work such as blood counts and urinalyses. A maximum of personal attention is given by the staff.

Prior to their arrival a detailed day by day program of educational activity for the entire eight weeks is prepared. This schedule includes patient rounds with staff members twice a week; attendance at weekly therapeutic conferences (the students prepare and present the case sum-

*The sixth in a series of articles prepared under the sponsorship of the Council on Undergraduate Medical Education of the American College of Chest Physicians.
**Executive Director, Trudeau-Saranac Institute, Trudeau, New York.

maries and statement of the problem); attendance at weekly admission and discharge conferences (they present the history and physical findings which they have worked up themselves); assisting at weekly progress clinic where they are assigned patients under staff supervision to evaluate progress; attendance twice weekly at x-ray film reading sessions; seminar type conferences thrice weekly with medical director and his associates, an informal question and discussion period for which students may sometimes prepare in advance for presentation of a subject; visits to staff meetings of other sanatoria; scrubbing in to observe surgical procedures; about two didactic lectures each week by staff members and consultants on various aspects of tuberculosis; assignment to laboratory to learn bacteriological techniques and observe methods of pulmonary function measurements; and attendance at weekly pulmonary physiology seminars. This means a rather full schedule but does leave time for reading and recreation on week-ends.

We have experienced no difficulty whatever with this group being afraid of tuberculosis. They are, of course, a picked group who have elected to come for this experience. In recent years at least one of our summer students has decided on thoracic surgery as a result of the interest which began here.

I feel the fact that the group is small, and we are able to give a considerable amount of personal attention, goes a long way toward arousing and keeping the interest of these students.

A third approach to the teaching of medical students was developed four years ago when an affiliation was arranged with the University of Vermont School of Medicine. During 10 months of the year two fourth year students are assigned to Trudeau each month. This means that approximately one-half of the class comes to Trudeau. In the past year arrangements have been made for the other half to be assigned to a nearby veterans tuberculosis hospital. Since the time these students spend with us is only one-half that of the summer students, they cannot be given as inclusive a curriculum as the latter. However, a scheduled program is arranged for each week which contains all the experiences given to the summer students but there are fewer didactic lectures. From the comments of the students, the program arranged for them has proved popular. One of the students here three years ago has come back to us this year as a resident physician.

When students first arrive they are given an orientation talk by a senior staff member on their approach and relationship to the patient, precautions, recommended reading and the aim of the period of study.

We do not expect to make phthisiologists but if we can make them aware, as general practitioners or specialists in other fields, of the possibility of tuberculosis in persons of any state of apparent health, economic status, age, etc.; of the fact that the treatment of tuberculosis is not static or stereotyped and requires planning and individualization; convince them that tuberculosis is not yet a vanished and conquered disease; and to realize that most patients are best treated by persons trained in the field and where the proper facilities are available, we feel that we have made a significant contribution to medical education and public health.

The President's Page

TWENTY YEARS OF PROGRESS

This is the first of several messages I plan to present to the members of the American College of Chest Physicians during the remainder of my term of office as your president. I think that it will be beneficial for all of us to know just what our College is doing, as well as what has been accomplished.

This year the College will celebrate twenty years of progress in the specialty of Diseases of the Chest. Prior to the organization of the American College of Chest Physicians, the term "Diseases of the Chest," as applied to the practice of our specialty, was little known. In a comparatively short period of time the College has popularized the term "Diseases of the Chest". Through our efforts, the American Medical Association and many state medical societies have instituted sections on Diseases of the Chest in their scientific assemblies and many more are considering the establishment of such sections. College chapters throughout the world regularly present scientific programs dealing with the broad aspects of Diseases of the Chest. The American Medical Association includes a section on Diseases of the Chest in its scientific exhibits and this exhibit has won gold, silver and bronze medals, as well as honorable mention, during the five years since its inception.

The field of Diseases of the Chest embraces many specialties and requires the expert services and knowledge of well-trained clinicians and thoracic surgeons, including pathologists, physiologists, roentgenologists, anethesiologists, bronchoesophagologists and allergists, as well as those internists who are concerned with cardiac and pulmonary conditions.

The American College of Chest Physicians has performed a real service to humanity by bringing together these highly trained scientists, each of whom plays an integral part in the teamwork essential in a multi-faceted specialty such as ours. This wealth of medical and surgical knowledge is represented by the membership of the College, as a growing international organization, with 4,555 members in 77 countries and territories throughout the world.

Our College Journal, which has been so appropriately titled by the founding fathers, DISEASES OF THE CHEST, enjoys a world-wide reputation for its splendid scientific contributions to medical literature. The Journal is eagerly sought by chest specialists throughout the world and is considered one of the leading publications in the field. The Editorial Board of the Journal does not wish to rest upon its laurels, but is making plans continuously to improve the Journal.

Not only have our members served humanity better, but in doing so, we have raised our own standards and we can be justly proud of our accomplishments as we enter into the third decade of our College.

In June we will commemorate with appropriate ceremonies our 20th Annual Scientific Assembly. Doctors Evarts A. Graham, Bixby Professor Emeritus, Washington University School of Medicine, St. Louis, Missouri, has kindly consented to inaugurate this occasion by presenting the first "Jacob Jesse Singer Lecture", sponsored by the California Chapter of the College. His subject will be "Remarks on the Etiology of Bronchogenic Carcinoma". An outstanding scientific program has been prepared. There will be the usual panel discussions, round table luncheons and other features which comprise our scientific assemblies. I am sure that you must be familiar with these excellent College activities.

I know that you will not want to miss the meeting this year and I am looking forward with pleasure to meeting you, your family and your associates in San Francisco.

Alvis E. Freer

College Chapter News

ALABAMA CHAPTER

Dr. V. H. Hill, Mobile, Governor of the College for Alabama, has arranged the following program to be presented on April 14 at 2:00 p. m. at the Admiral Semms Hotel, Mobile:

"Mycotic Infections of the Lungs," Alvis E. Greer, Houston, Texas, President, American College of Chest Physicians.

"Management of Mediastinal and Para Mediastinal Tumors," DeWitt C. Daughtry, Miami, Florida.

"Recent Advances in Cardiac Surgery," Osler A. Abbott, Atlanta, Georgia, Governor of the College for Georgia.

At 8:00 p. m. a dinner meeting will be held at the hotel at which time the organization of the Alabama Chapter will be effected.

ARIZONA CHAPTER

The Arizona Chapter of the College will hold its annual meeting in conjunction with the Arizona State Medical Society meeting at the San Marcos Hotel in Chandler, April 28. At the chapter luncheon meeting, Dr. Harold G. Trimble, Oakland, California, will speak on "Therapy in Pulmonary Tuberculosis—A Study of 10 Cases by 100 American Consultants." Following the luncheon, Dr. Gerald L. Crenshaw, Oakland, California, will speak on "Coin Lesions" and Dr. Hurley L. Motley, Los Angeles, California, will speak on "Pulmonary Function Tests."

FLORIDA CHAPTER

The sixth annual meeting of the Florida Chapter of the College will be held in Hollywood, April 25, at the time of the Florida Medical Association meeting. The program is as follows:

9:30 a. m.: Business meeting.

10:00 a. m.: Scientific session.

"Cancer of the Larynx," Nathaniel L. Levin, Miami.

"Electrolyte Balance in Congestive Heart Failure," David A. Newman, Palm Beach.

"Funnel Chest Correction," DeWitt C. Daughtry and John G. Chesney, Miami.

"Recognition and Management of Child Allergy," Milton B. Cole, St. Petersburg.

"Extraperiostial Lucite Ball Plombage," Burnett Schaff, Jack Reiss and George C. Baum, Coral Gables.

Luncheon — Guest speaker: Alvis E. Greer, Houston, Texas, President, American College of Chest Physicians: "A Discussion of Certain Preliminary Aspects of Pulmonary Mycotic Disease."

2:00 p. m.: Panel Discussion — "Chronic Cor Pulmonale," Morris Dick, George E. Baum and Jack Reiss, Coral Gables. *Moderator:* M. Jay Flipse, Miami.

3:00 p. m.: X-ray conference.

MISSOURI CHAPTER

A joint meeting of the Missouri Chapter of the College and the Missouri Trudeau Society, in conjunction with the meeting of the state medical society, will be held at the Statler Hotel, St. Louis, April 4. Following a morning business meeting and luncheon, the scientific program will be presented.

"Miliary Lesions in the Lung," Sydney Jacobs, New Orleans, Louisiana.

"Pediatric Chest Conditions," James King, St. Louis.

"Pneumoconiosis," John Wyatt, St. Louis.

X-ray Conference — Hyman Senturia, St. Louis, moderator.

OHIO CHAPTER

The Ohio Chapter will hold its annual meeting in Columbus, April 14 at the Deshler-Hilton Hotel, in conjunction with the Ohio State Medical Association Meeting. Following a business meeting and luncheon, Dr. Neil Andrews, Columbus, will speak on "Surgery in the Diagnosis of Pulmonary Diseases."

TENNESSEE THORACIC SOCIETY

The Tennessee Thoracic Society, sponsored by the American College of Chest Physicians, will present the following program at its second annual meeting to be held in Nashville, April 21, in conjunction with the state medical association meeting:

"Diagnosis and Treatment of Pulmonary Nodules,"
Foster Hampton, Jr., Chattanooga.

"Spontaneous Pneumothorax," Sheldom E. Domm, Knoxville.

"The Treatment of Carcinoma of the Esophagus,"
Felix Hughes, John Fox and John Kehne, Memphis.

JAPANESE CHAPTER

The second annual meeting of the Japanese Chapter of the College was held in Tokyo, January 31 with an attendance of 150 physicians. New officers elected at the meeting are: Jo Ono, Tokyo, President; Kingo Shinoi, Tokyo, Vice-President; Osamu Kitamoto, Tokyo, Secretary-Treasurer. The following scientific program was presented:

"An Appraisal of Pneumothorax Treatment in Pulmonary Tuberculosis,"
Yasuyuki Kano.

"Impressions of the Annual Convention of the American College of Chest Physicians in 1953," Chigashi Suzuki.

"Recent Studies on BCG," Toshiaki Ebina.

"The Immuno-serological Reaction in Tuberculosis," Osamu Kitamoto.

COMMITTEE ON NOMINATIONS

Elections for offices expiring in June, 1954 will be held at the Fairmont Hotel, San Francisco, June 19. Recommendations for elective offices may be addressed to the chairman of the Committee on Nominations, Dr. Andrew L. Banyai, Muirdale Sanatorium, Milwaukee, Wisconsin. Other members of the committee are Dr. William S. Conklin, Portland, Oregon and Dr. Alexander Libow, Miami Beach, Florida.

College News Notes

Dr. Harry Shubin, Philadelphia, Pennsylvania, has recently been appointed Chief of Service, Department of Chest Diseases, Philadelphia General Hospital Northern Division. Dr. Shubin is also Chief of Service at the Rush Hospital.

Dr. Albert H. Andrews, Jr., Chicago, Illinois, Assistant Clinical Professor of Bronchoesophagology, University of Illinois College of Medicine, has been elected President of the Otolaryngologic Alumni Association of the University of Illinois.

Dr. Giovanni L'Eltore, Rome, Italy, was recently elected as a Deputy to the Italian Parliament.

Dr. R. A. Dorner, Des Moines, Iowa, spoke on "Cancer of the Lung" at a recent meeting held at the Ottumwa Hospital under the joint sponsorship of the State Department of Health, Iowa Division of the American Cancer Society, and the Iowa State Medical Society.

At the Annual Meeting of the Board of the Detroit Tuberculosis Sanatorium, the name of the hospital was changed to "The Chest and General Hospital of Detroit." Dr. William A. Hudson, Detroit, President-elect of the College was re-elected to the Board of Directors. Dr. Willard Boyden Howes, Detroit, Regent of the College for Michigan, will continue as the Medical Director and Superintendent of the hospital.

ANNUAL MOTION PICTURE SESSION

The annual motion picture session on diseases of the chest will be presented at the 20th Annual Meeting of the College on Friday evening, June 18, at the Fairmont Hotel, San Francisco. Members who have films which would be of interest at the meeting are invited to communicate with Dr. Paul H. Holinger, 700 North Michigan Avenue, Chicago, Illinois, Chairman of the Committee on Audiovisual Aids which is in charge of organizing the motion picture program. Please give all pertinent information concerning the film, such as running time, color or black and white, silent or sound, etc., and it would be helpful if a description of the film, not to exceed 100 words, is included. All films must be approved by the Committee before accepted for presentation at the College meeting.

THIRD INTERNATIONAL CONGRESS, BARCELONA, SPAIN

The Council on International Affairs of the American College of Chest Physicians reports that requests for places on the scientific program to be presented in Barcelona, October 4-8, 1954, have been received from 150 members of the College in 34 countries. Delegates from 44 countries have notified the Council that they will attend this important Congress. If you plan to attend, please notify the Executive Director, American College of Chest Physicians, 112 East Chestnut St., Chicago 11, Illinois, U.S.A.

MEDICAL SERVICE BUREAU

Position Wanted

Full-time staff position wanted with research facilities in pulmonary or cardiopulmonary diseases. Foreign graduate, F.C.C.P., 35 years of age, with training in this country as well as abroad in tuberculous and non-tuberculous diseases of the chest. Presently completing postgraduate work in large eastern medical center. Available after July 1, 1954. Please address all inquiries to Box 282B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

20th ANNUAL MEETING OF THE COLLEGE, SAN FRANCISCO, JUNE 17-20

IMPORTANT — Have you made your hotel reservations?

If not, please write immediately to the **AMA** Housing Bureau, Room 200, 61 Grove Street, San Francisco 2, California, and request reservations for the 20th **ANNUAL MEETING, AMERICAN COLLEGE OF CHEST PHYSICIANS**, Fairmont Hotel, June 17-20. Be sure to give arrival and departure dates and *enclose deposit check in the amount of $10.00* made payable to the **AMA** Housing Bureau. — **WRITE AT ONCE.**

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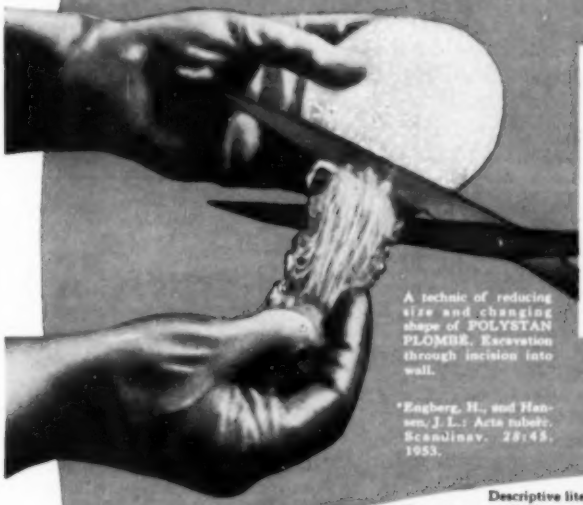
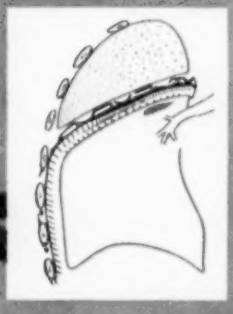


A technic of reducing size and changing shape of POLYSTAN PLOMBE. Excavation through incision into wall.



Extraperiosteal pneumolysis. Intercostal circulation preserved. POLYSTAN PLOMBE *in situ*.

*Engberg, H., and Hansen, J. L.: Acta tuberc. Scandinav. 28:45, 1953.

Descriptive literature and complete bibliography available upon request.
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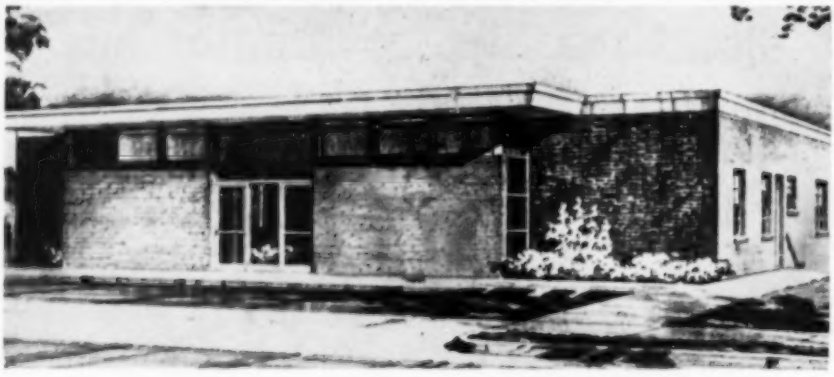

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POSTGRADUATE COURSE

7th Annual Postgraduate Course on Diseases of the Chest
Bellevue-Stratford Hotel, Philadelphia, Pennsylvania, March 15-19, 1954.

CHAPTER MEETINGS

Missouri Chapter, St. Louis, April 4.
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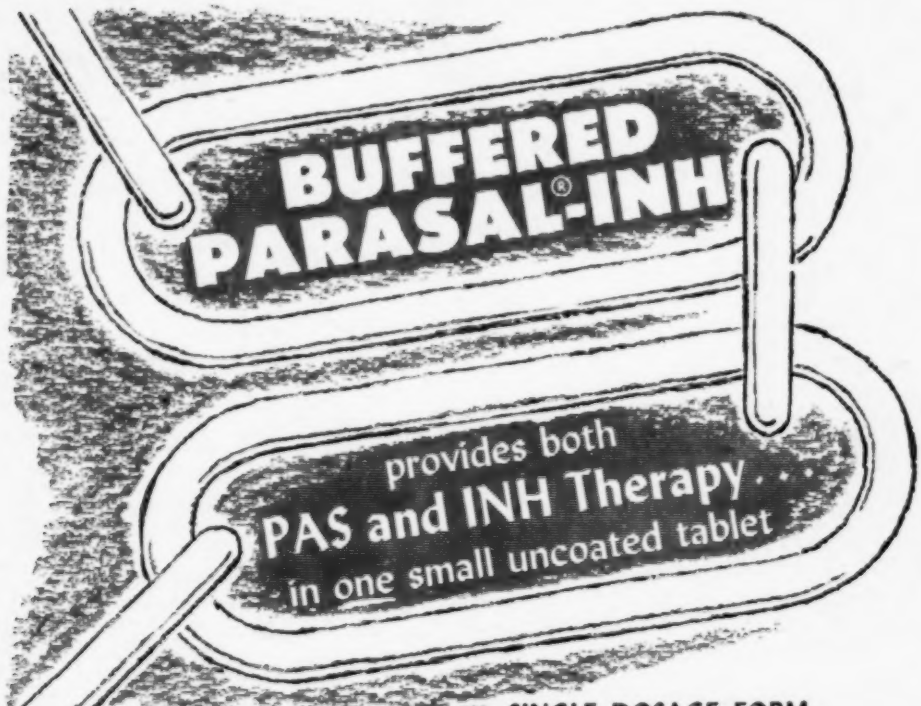

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